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Molecular prognostic and predictive factors of breast cancer

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The Faculty of Medicine, University of Helsinki, uses the Urkund system (plagiarism recognition) to examine all doctoral dissertation.

To my late grandfather, Aqaee

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Abstract

Despite advances in the early detection and treatment of breast cancer, it remains a challenge to identify which patients may experience a poor prognosis or respond poorly to treatment. Familial predisposition is a major risk factor of breast cancer and, perhaps, a modifier of patients' survival. There is also evidence suggesting that hereditary factors may impact a patient's response to treatment. However, the magnitude of the effect, and the molecular mechanism behind it, is largely unknown.

In Finland, over 4,000 women on average are annually diagnosed with breast cancer and the majority of them undergo chemotherapy; they may or may not respond to the treatment. It is challenging to identify germline markers and tumor molecular profiles, which objectively predict prognosis and treatment response, and translate this information into cancer therapy.

The aim of this thesis was to identify prognostic and predictive markers in breast cancer by investigating cancer-related networks as well as candidate genes of regulatory networks in invasive breast cancer cases. Taking both a network analysis approach as well as a candidate gene study, clinicopathological and survival association analyses were performed to (I) study the association of germline variations in *TP53* network genes with breast cancer patients' survival and treatment outcome; (II) investigate the impact of two-SNP interaction of NF-κB signaling network on predicting patients' survival; (III) evaluate the association of NQO1 protein expression and NF-κB activation with clinicopathological features of the tumors, patients' survival, and treatment outcome; and (IV) study the role of the miR-30 family in breast cancer patients' survival and drug response.

The germline variations were studied in collaboration with the Breast Cancer Association Consortium (BCAC). In Study I, the variations were initially analyzed in a set of DNA samples from 925 invasive breast cancer cases from Helsinki Breast Cancer Study (HEBCS) included in BCAC, and were further analyzed in pooled data of 4,701 cases from four independent studies (including HEBCS) contributing to BCAC. In Study II, the germline variations were studied in extensive pooled data of 30,431 cases from 24 independent studies participating in BCAC. In Studies III and IV, the tumor samples for immunohistochemical and miRNA *in situ* hybridization of 1,240 cases were from two series of 884 unselected Finnish invasive breast cancer patients and an additional 542 familial cases. Gene expression analysis was performed using microarray data of total RNA from 187 fresh frozen primary breast cancer tumors. Drug sensitivity screening tested the influence of miR-30 family members on the response of human breast cancer cell lines to two drugs, doxorubicin and lapatinib.

In Study I, a significant interaction effect was found between germline variations in TP53-related genes, *PRKAG2* (rs4726050) and *MDM2* SNP309, with *PRKAG2* (rs4726050) rare G allele showing a dose-dependent impact for superior breast cancer survival only among the *MDM2* SNP309 rare G allele carriers. Also, *PPP2R2B* (rs10477313) rare A allele predicted increased survival after hormonal therapy. Further studies are warranted to clarify the impact of *PRKAG2* and *PPP2R2B* on patients' survival.

In Study II, the SNP-SNP interaction test in the NF-κB activating pathway found two interacting SNP pairs, rs5996080-rs7973914 and rs17243893-rs57890595, which was associated with patients' survival under recessive and dominant models of inheritance, respectively. While rs5996080 and rs7973914 were included in the study for representing the haplotype block harboring NF-κB activating genes, *BAFFR* and *TNFR1/3*, they physically reside in *SREBF2* and *SCNN1A*, thus, the interacting effect found between these two loci may represent either of the genes. The dominant SNP pair, rs17243893 and rs57890595, represented *TRAF2* and *TRAIL-R4*. Based on the published function of the interacting genes, and the *in silico* analysis of this study, the survival association of the identified SNP pairs may be a result of interplay between these gene pairs and their downstream influence on the dynamic of canonical and non-canonical NF-κB pathways.

In Study III, the immunohistochemical staining analysis of NQO1 expression and NF-κB nuclear localization (inferred activity) did not find significant association between either of the proteins and patients' survival or treatment outcome. However, an inverse correlation between NQO1 expression and NF-κB activity was observed in breast cancer tumors. The NQO1/NF-κB inverse correlation was also reflected in their association with ER status, as well as their correlation with gene expression.

In Study IV, a significant association was found between the high expression of miR-30d and longer metastasis-free survival, particularly in subgroups of patients with high proliferative tumors, ER negativity, HER2 positivity, and among those who received chemotherapy. However, the high expression of miR-30 appeared to also correlate with the characteristics of aggressive tumors, i.e. higher grade, positive nodal status, and high proliferation (estimated by high Ki67). In a drug sensitivity screening test of all miR-30 family members, miR-30a–e sensitized the human breast cancer cell lines to doxorubicin. Also, in the HER2-positive HCC1954 cell line, miR-30d sensitized the cells to lapatinib. The pathway enrichment analysis of miR-30 family members in the METABRIC gene expression dataset revealed that high levels of miR-30 family occurred simultaneously with low expressions of genes involved in cell movements, consistent with the observed association with longer metastasis-free survival.

The result of this work suggests prognostic/predictive potentials for candidate genes in cancer-related networks (TP53 and NF-κB), as well as regulatory networks (microRNAs), which warrant further investigations.

List of original publications

This thesis is based on the following publications, which are referred to in the text by their Roman numerals:

I Jamshidi, M., Schmidt, M.K., Dork, T., Garcia-Closas, M., Heikkinen, T., Cornelissen, S., van den Broek, A.J., Schurmann, P., Meyer, A., Park-Simon, T.W., Figueroa, J., Sherman, M., Lissowska, J., Keong, G.T., Irwanto, A., Laakso, M., Hautaniemi, S., Aittomaki, K., Blomqvist, C., Liu, J. & Nevanlinna, H. 2013, "Germline variation in TP53 regulatory network genes associates with breast cancer survival and treatment outcome", *International journal of cancer. Journal international du cancer,* vol. 132, no. 9, pp. 2044-2055.

II Jamshidi, M., Fagerholm, R., Khan, S., Aittomaki, K., Czene, K., Darabi, H., Li, J., Andrulis, I.L., Chang-Claude, J., Devilee, P., Fasching, P.A., Michailidou, K., Bolla, M.K., Dennis, J., Wang, Q., Guo, Q., Rhenius, V., Cornelissen, S., Rudolph, A., Knight, J.A., Loehberg, C.R., Burwinkel, B., Marme, F., Hopper, J.L., Southey, M.C., Bojesen, S.E., Flyger, H., Brenner, H., Holleczek, B., Margolin, S., Mannermaa, A., Kosma, V.M., kConFab Investigators, Van Dyck, L., Nevelsteen, I., Couch, F.J., Olson, J.E., Giles, G.G., McLean, C., Haiman, C.A., Henderson, B.E., Winqvist, R., Pylkas, K., Tollenaar, R.A., Garcia-Closas, M., Figueroa, J., Hooning, M.J., Martens, J.W., Cox, A., Cross, S.S., Simard, J., Dunning, A.M., Easton, D.F., Pharoah, P.D., Hall, P., Blomqvist, C., Schmidt, M.K. & Nevanlinna, H. 2015, "SNP-SNP interaction analysis of NF-kappaB signaling pathway on breast cancer survival", *Oncotarget,* vol. 6, no. 35, pp. 37979-37994.

III Jamshidi, M., Bartkova, J., Greco, D., Tommiska, J., Fagerholm, R., Aittomaki, K., Mattson, J., Villman, K., Vrtel, R., Lukas, J., Heikkila, P., Blomqvist, C., Bartek, J. & Nevanlinna, H. 2012, "NQO1 expression correlates inversely with NF-kappaB activation in human breast cancer", *Breast cancer research and treatment,* vol. 132, no. 3, pp. 955-968.

IV Expression of miR-30 family members associates with improved breast cancer survival and treatment outcome (Submitted)

Maral Jamshidi, Rainer Fagerholm, Taru A Muranen, Sippy Kaur, Swapnil Potdar, Sofia Khan, Eliisa Netti, John-Patrick Mpindi, Bhagwan Yadav, Johanna I Kiiski, Kristiina Aittomäki, Päivi Heikkilä, Jani Saarela, Ralf Bützow, Carl Blomqvist, Heli Nevanlinna

Abbreviations

Gene names are written in *italics*.

AKT	AKT serine/threonine kinase 1
APC	APC, WNT signaling pathway
AT	ataxia telangiectasia
ATM	ataxia telangiectasia mutated
BARD1	BRCA1 associated RING domain 1
BCAC	Breast Cancer Association Consortium
BAFFR	B-cell activating factor receptor
BRCA1	breast cancer gene 1
BRCA2	breast cancer gene 2
BRCT	BRCA1 carboxy-terminal repeat
BRIP1	BRCA1 interacting protein 1
CCNG1	cyclin G1
CHEK2	checkpoint kinase 2
CI	confidence interval
CISH	chromogenic *in situ* hybridization
CMF	cyclophosphamide, methotrexate, and fluorouracil
DNA	deoxyribonucleic acid
ER	estrogen receptor
HR	hazard ratio
FISH	fluorescence *in situ* hybridization
HER2/ERBB2/neu	human epidermal growth factor receptor 2
GEX	gene expression
GWAS	genome-wide association study
M	metastasis at time of diagnosis
MDM2	mouse double minute 2 homolog
MLH1	mutL homolog 1
N	nodal status
NF-κB	nuclear factor kappa B
NQO1	NAD(P)H:quinone oxidoreductase
PgR/PR	progesterone receptor
PIAS1	protein inhibitor of activated Stat1
PPP2R2B	PP2A, regulatory subunit B, beta isoform
PR	progesterone receptor
PRKAG2	AMP-activated protein kinase γ2 subunit
PTEN	phosphatase and tensin homolog
SNP	single-nucleotide polymorphism
T	tumor size
TNFR1	TNFR superfamily member 1
TNFR3	TNFR superfamily member 3
TOP2A	topoisomerase II alpha
TP53	tumor protein p53
TRAIL-R4	TNF-related apoptosis ligand receptor 4
UTR	untranslated region
YWHAQ	14-3-3ε

1 Introduction

Breast cancer is the most frequently diagnosed cancer among women worldwide, accounting for more than 1 in 10 new cancer cases (Bray et al., 2018). Familial predisposition is a significant breast cancer risk factor. Women with two or more breast cancer patient relatives have a 2.5-fold increased risk of developing the disease.

The mortality rate of breast cancer has been decreased since the early 1990s thanks to early detection and significant advances in cancer treatment (Brewer et al., 2017). Breast cancer prognosis varies considerably based on the characteristics of the tumor, and is highly dependent on clinical and pathological factors such as the status of axillary lymph nodes, the expression of estrogen receptor (ER) or HER2 and the status of metastasis. The ER and HER2 status also assist the therapy decisions, i.e. ER-positive tumors are responsive to hormonal therapy, such as tamoxifen, and HER2-positive tumors are more likely to respond to anti-HER2 agents, such as trastuzumab and lapatinib. If clinically appropriate, both groups may also receive chemotherapy. Patients without hormone receptor or HER2 positivity only receive chemotherapy. However, many patients do not respond to therapy and a significant number of responsive patients will eventually develop drug resistance (Waks & Winer, 2019). Therefore, additional reliable biomarkers are required to identify patient groups with poor prognosis and to predict and facilitate therapeutic decision-making, which in turn leads to improved cancer management and better patient care.

While the impact of germline mutation on breast cancer risk is rather well established (Brewer et al., 2017), the contribution of the hereditary component to the prognosis of breast cancer and the molecular mechanism behind it is yet to be elucidated. However, germline variations in candidate cancer-related genes have been suggested to associate with patients' survival.

This thesis studied an extensive set of invasive breast cancer patients to investigate the germline variations in cancer-related pathways (i.e. TP53 and NF-κB), and expression of regulatory elements (i.e. miR-30 family), for their association with patients' survival, also stratified by patient subgroups based on features of the tumor, and with treatment outcome, as well as their correlation with the clinicopathological feature of the tumors. Additionally, a drug sensitivity screening tested the impact of the miR-30 family on sensitizing the breast cancer cell lines to doxorubicin and lapatinib.

2 Review of the literature

2.1 Cancer

Cancer is the second cause of death following heart disease. The global burden of cancer is increasing due to sociodemographic and lifestyle changes, as well as the aging of the world population. Nearly 18 million new cancer cases were registered worldwide in 2018; of these, 9.4 million were male and 8.6 million were female. A total of 9.4 million deaths due to cancer are estimated to have occurred in 2018, including 5.3 million male and 4.1 million female. Lung, breast, and colorectum are the most frequent cancer sites and the leading cause of cancer death (Globocan http://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf).

Cancer arises from genetic mutation in the DNA, which occurs for a variety of reasons. The most-studied known or suspected risk factors for cancer include age, alcohol, cancer-causing substances, chronic inflammation, diet, heredity, hormones, immune suppression, infectious agents, obesity, radiation, sunlight, and tobacco. Also, about 15% of cancers stem from viral infections, e.g. human papillomavirus. Some cancer risk factors are uncontrollable, such as aging and heredity, and some are controllable, such as tobacco products, sunlight, and diet. Although many cancers are not preventable, a major reduction in cancer associated mortality is achievable through early detection (and changes in lifestyle), for instance, cervical, breast and prostate cancers can be slowed or even eradicated with early detection (Allemani et al., 2018).

2.1.1 Tumorigenesis and the biology of cancer

For the living organism to grow, repair, and reproduce, cells need to retain the ability to replicate and divide. The process of cell division is a small fraction of the cell cycle in which the DNA molecules duplicate and segregate into daughter cells under a well-orchestrated replication mechanism. Despite the elaborate genome maintenance systems that control the replication machinery, cells may deviate from the normal constraints of division and proliferate uncontrollably, which results in tumor formation. Tumors which are not cancerous are known as benign; cancers that grow locally without spreading to surrounding tissues are classified as carcinoma *in situ*; and those with the ability to invade neighboring tissues and spawn metastasis through the body are described as malignant, commonly known as cancerous. Benign tumors are rarely life threatening; however, they can cause clinical problems if their expansion causes them to press on vital structures (e.g. blood vessels, nerves), or if they cause the over-release of hormones (e.g. excessive release of thyroid hormone). In general, benign tumors are often slow growing in nature, and more differentiated compared to the cancerous tumors.

Cancer can originate from almost all cell types, however, the most common human cancers rise from epithelial cells — the carcinomas. Based on their shape and biological function, normal epithelia and the carcinomas originating from them fall into two categories of squamous cell carcinoma and adenocarcinoma. Squamous cell carcinomas, such as the keratinocyte carcinoma of the skin, arise from the often-flattened epithelial sheets lining the top layer of skin, cavities, and channels to protect the underlying tissues. Adenocarcinomas form in the substance-secreting glands and are commonly found in the breast, colon, pancreas, stomach, prostate, endometrium, and ovary.

Epithelia in the lung, uterus, and cervix have the capability to transform into adenocarcinoma or squamous cell carcinoma or both. As for non-epithelial malignant tumors, the major classes include (1) sarcomas, which arise from mesenchymal connective tissues that make up bones, as well as soft tissues such as muscles, tendons, and blood vessels, (2) hematopoietic cancers, which originate from the precursors of blood-forming tissues, including the cells of the immune system, and (3) neuroectodermal malignant tumors, which emerge from the central and peripheral nervous system.

From the completely benign to the highly malignant, tumors represent an increasing degree of tissue abnormality, which suggests that tumor progression is a multistep process. For a normal cell to transform to cancer, it must acquire generic tumorigenic competence, also described as a hallmark of cancer (Hanahan & Weinberg, 2011). The hallmarks of cancer include sustaining proliferative signaling, i.e. applying alternative mechanisms that may deregulate division and growth signals in order to operate chronic proliferation and thus tumor initiation and growth. Excessive proliferation also involves evading growth suppressors, as well as protecting incipient cancer cells from programmed cell death, termed apoptosis. Of the diverse strategies tumor cells evolve to attenuate the apoptosis circuitry, the most common is the loss of tumor protein p53 (TP53), a tumor suppressor function which will be discussed in section 2.5.

In normal cells, the replication rate is controlled also through the length of telomeric DNA: the telomere length declines upon each cell generation until it becomes too short to protect the chromosome end, which results in either replicative senescence or crisis. To enable replicative immortality, tumor cells must maintain a sufficient length of telomere and avoid crisis-induced cell death. Further, as the cancer cells proliferate and become more aggressive, they also enable angiogenesis — i.e. blood vessel formation — to grant nutrition, oxygen and waste disposal. When this occurs, the tumor is referred to as invasive, because the cells can now break off and enter the blood stream and invade other tissues and organs; this co-opt developmental process is termed metastasis.

Invasion and metastasis are the essential differences between the benign, and often harmless, tumors and the cancerous ones. They count for virtually 90% of cancer death and represent the major unsolved problem of cancer pathogenesis. The majority of small tumors are destroyed by the innate immune system. However, occasionally tumor cells evade detection and destruction by the immune system, to become more fit and survive in their host. To grow beyond their limit size, cancer cells divide rapidly, thus, compared to their generally quiescent cells of origin, they need more energy, oxygen, and biomaterials. In the past decade, it became increasingly clear that cancer cells reprogram their energy metabolism. However, whether reprogramming the energy metabolism and evading immune system destruction are general to many forms of cancer or selective for few remains unclear.

2.1.2 Cancer genes and mutations

Mutations in cancer genes enhance cancer risk or promote cancer development. Traditionally, cancer genes involve two types of growth-controlling genes: (1) oncogenes which promote cell growth and/or motility and are usually upregulated in cancer cells, and (2) tumor suppressor genes which suppress cell growth and/or motility and are frequently deactivated in cancer cells (Ponder, 2001; Weinberg, 1989).

Oncogene mutations contributing to cancer are typically gain-of-function mutations which render the gene over-activation or activation under conditions in which the wild-type gene is silent. Oncogene activation is driven from various types of mutations, including genomic rearrangement and chromosomal translocations (e.g. the MYC gene family), gene amplification (e.g. *ERBB2* also known as *HER2/neu*), and base substitution/insertion/deletion (e.g. *PIK3CA*), which either directly result in over expression of the cancer-contributing gene or impact its regulation and activation process. It appears that a single oncogene activating mutation is enough to provide unlimited growth advantage to the cell, in spite of the continued presence of a wild-type allele. However, the growth advantage rendered by oncogenes can be impaired by inactivation of a single oncogene, a phenomenon referred to as oncogene addiction, which provides therapeutic potentials (Weinstein & Joe, 2008). Although oncogenes are dominant mutations, it is worthy of note that cancer is a multistep mutation process, and single mutations may develop tumor but are not typically sufficient to produce cancer. While a single oncogene mutation is sufficient to develop cancer in immortalized laboratory cells which are already sensitive to oncogenes, we know now that an accumulation of 3-20 driver mutations are required to make a fully developed cancer in normal cells in a human's body (Tomasetti et al., 2015).

The partial or total inactivation of the tumor suppressor genes is typically the result of loss-of-function mutations, whereas gene amplification and chromosomal translocation are rarely found in these genes. The inactivation is frequently driven from truncation of the gene open reading frame (ORF) through nonsense mutation, small insertion/deletion, or splice site mutation. Loss-of-function mutation in tumor suppressor genes generally act recessively at the cellular level, which means that the mutated allele is masked by the wild-type allele and therefore, as suggested in Knudson's "two-hit" hypothesis (Knudson, 1971), the cellular phenotype of a mutated tumor suppressor only manifests when both alleles are altered. An exception to this mechanism is another pathological phenotype referred to as haploinsufficiency, where one wild-type allele is not adequate to carry out the protein function (e.g. *BRCA1*-haploinsufficiency). An additional exception is the non-mutational impairment of the wild-type allele referred to as the dominant negative effect of the mutated allele which blocks the function of the wild-type one. Dominant negative effect is common in *TP53* pathogenesis caused by missense mutation (Srivastava et al., 1993).

Every tumor carries thousands of genetic and epigenetic mutations, however, only a very small portion of these mutations render the tumor cell a growth advantage over the surrounding cells. Based on their tumorigenic consequences, the mutations are identified as driver and passenger. Driver mutations endow the tumor cells an essential fitness advantage in their microenvironment, and thus are selected during clonal evolution. Passenger mutations provide no such benefit and occur by chance before or during the process of tumorigenesis and can also be found in normal

proliferative tissues. Since the vast majority of mutations (97%) (Lawrence et al., 2014) in cancer are passengers, it is challenging to distinguish them from driver mutations. There is no compelling evidence to suggest that the accumulation of passenger mutations contributes to tumor progression, but whether they are deleterious to cancer growth and metastasis remains to be concluded (Stratton, Campbell & Futreal, 2009; McFarland et al., 2017).

Another classic categorization of tumor suppressor genes includes:

(1) gatekeepers which directly suppress cell outgrowths and, if mutated, highly elevate the risk of tumor development. The characteristic example includes the gatekeeping mutation in *APC* which associates with the initiation of colorectal cancer;

(2) caretakers which participate in DNA repair to maintain genome stability. Examples of caretaker genes are the breast cancer susceptibility genes *BRCA1* and *BRCA2*;

(3) landscapers which maintain the normal tissue architecture and homeostasis and when mutated result in a tumor-prone microenvironment defect. For instance, mutation in *SMAD4* contributes to formation of colorectal cancer by altering the tissue structure of colorectal mucosa and therefore providing a tumor-prone landscape (Vogelstein et al., 2013; Kinzler & Vogelstein, 1997).

In the context of genetics, the human body consists of two types of cells: germ cells and somatic cells. Germ cells are the cells of the reproductive system, which give rise to female and male gametes, also known as oocyte and sperm, respectively. All other cells in the body are somatic cells. If the cancer gene mutation arises in the lineage of germ cells (the germline) it will be carried in every cell of the individual who inherited it, whereas if the cancer gene mutation arises in the somatic cells, the mutation is not passed through generations. In this context, the mutations in cancer genes are either acquired through inheritance via the germline, or spontaneously via somatic mutation or virus infection. Although germline mutations in cancer susceptibility genes significantly increase the cancer risk in individuals who inherit them, they impart only a subset of all cancer risks. The heritable mutations discovered in germlines are attributable primarily to tumor suppressor genes, whereas nearly all mutations that convert proto-oncogenes to oncogenes are acquired by somatic mutations and, in general, are not identified in the germline of a cancer-prone family. Thus, they are unlikely to play a major role in hereditary cancer predisposition, which will be described in the following section (Ponder, 2001; Oosterhuis & Looijenga, 2019).

2.1.3 Hereditary predisposition to cancer

An entire set of genes is identified whose mutations contribute to hereditary cancer syndromes. However, the degree of penetrance — that is, the likelihood of cancer development conferred by these genes — varies+. During the 1980s and 1990s, linkage analysis and positional cloning resulted in identification of highly penetrant cancer susceptibility genes, including *BRCA1* and *BRCA2* (for breast and ovarian cancer), *APC* (for colorectal cancer), *MSH1* and *MLH2* (for Lynch syndrome), and *CDKN2A* (for melanoma); most of these are involved in DNA damage repair or cell cycle control (Foulkes, 2008; Easton et al., 2015). The high penetrance cancer associated mutations

are infrequent and their prevalence varies between populations, and they only explain a subset of cancer heritability. Presumably there are other germline cancer genes which impact overall cancer risk but, due to the lesser penetrance they confer, their attributable risk is difficult to quantify, and they are hard to identify by linkage analysis due to incomplete familial segregation. Alternative approaches — such as candidate gene studies and GWAS — were therefore applied to facilitate the discovery of moderate and low penetrant cancer genes which, despite their presence also in the general population, may impact the individual's risk and survival after breast cancer (Michailidou et al., 2013, 2017).

In addition to penetrance and attributable risk, the impact of inheriting germline cancer genes is assessed by several metrics. These commonly include the relative risk (risk ratio), which is the probability of cancer occurring in mutation carriers divided by the probability of cancer occurring in the general population; and the odds ratio, which represents the efficacy of the mutant allele in developing cancer and is measured by the odds that an individual with the mutation develops cancer divided by the odds of an individual without the mutation developing cancer. The importance of assessing cancer risk (and survival) in individuals with a family history of cancer is manifested in the success of cancer screening, available genetic testing, and counseling in oncology clinics and clinical genetics departments. These productive approaches promote the early detection of cancer, and thus reduce the cancer caused mortality rate. Additionally, they aid the process of decision making in taking aggressive preventive measures such as breast mastectomy. While cancer treatment is the major field of study in cancer research, in the future we hopefully have fewer cancers to treat because we will be able to prevent some (Merkow et al., 2017).

2.2 Breast cancer

2.2.1 Epidemiology

Breast cancer is by far the most commonly diagnosed neoplasm in women and the leading cause of cancer death among women worldwide (Figure 1). Breast tumors occur in men too, but much less frequently than in women. In 2018, about 2 million new cancer cases were diagnosed among women worldwide (Globocan http://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf). The overall breast cancer incidence rate (i.e. the number of newly diagnosed cases in a given time period) is higher in developed countries and, traditionally, lower in many low–middle income countries. The diversity of incidence rates implicates the difference in awareness, prevalence, adequate screening methods, and lifestyle-related risk factors such as obesity, smoking, reproductive patterns, hormonal therapy after menopause, etc. However, economic transitions, recent changes in reproductive patterns (such as later age at first childbirth), and fewer childbirths appear to increase the incidence rate in low–middle income countries. The mortality rate, too, varies globally due to the availability of resources which impact survival rate by influencing the prevention, early detection, and treatment approaches. The current five-year survival rate is 85% or higher in high income countries and 60% or lower in most low–middle income countries, primarily due to late detection and inadequate health services (Allemani et al., 2015). In Finland, 4,961 new breast cancer cases were diagnosed in 2016, which account for almost 32% of all new cancer cases

in the country. Figure 2 illustrates the trends of cancer incidence (2a) and mortality (2b) rates among women in Finland between 1953 and 2016.

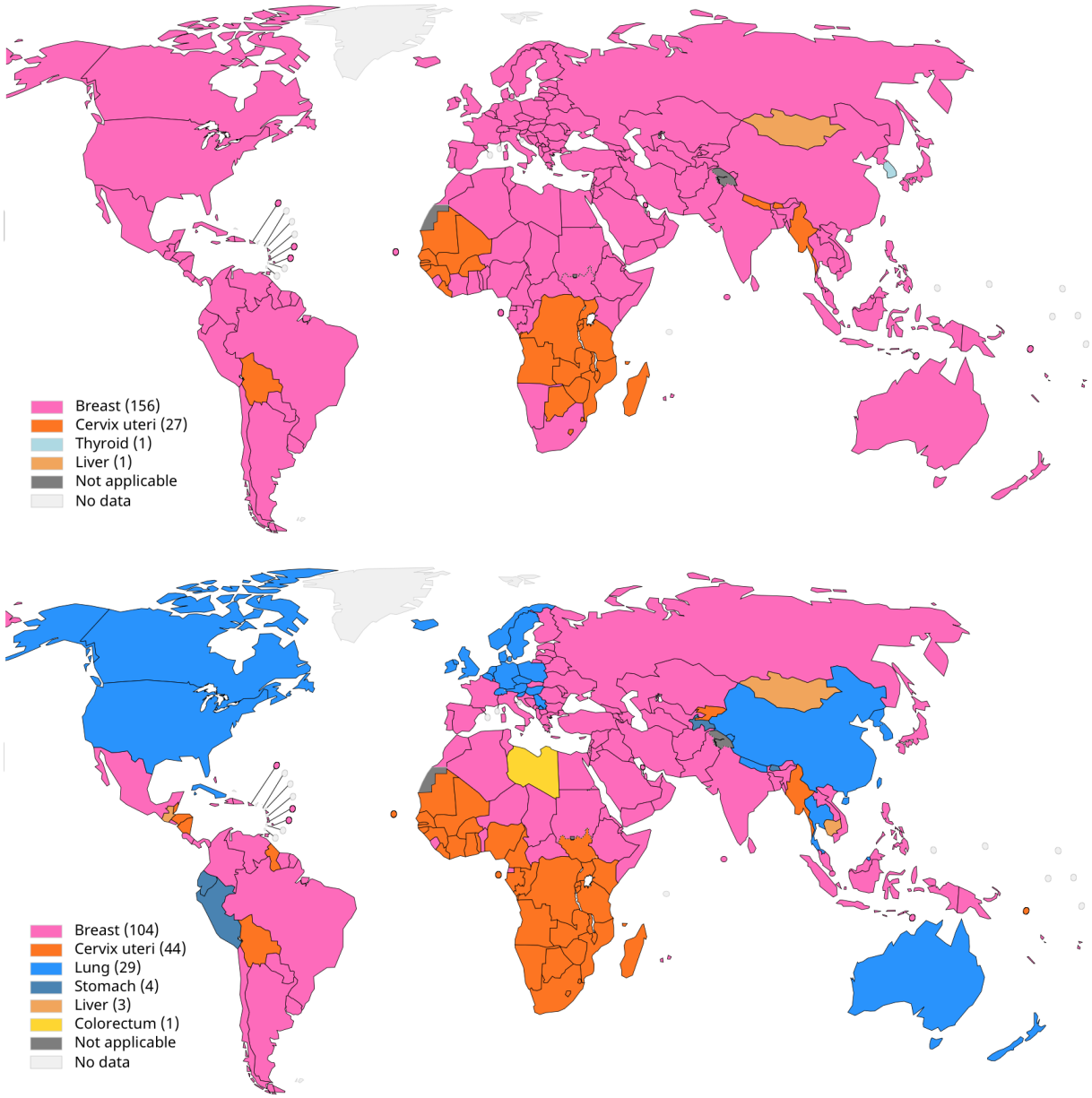


Figure 1. Top: most common cancer site per country, estimated age standardized incidence rate (world), 2018, females, all ages. Bottom: most common cancer site per country, estimated age standardized mortality rate (world), 2018, females, all ages. Source: Cancer Today-IARC (International Agency for Research on Cancer), http://gco.iarc.fr/today/home.

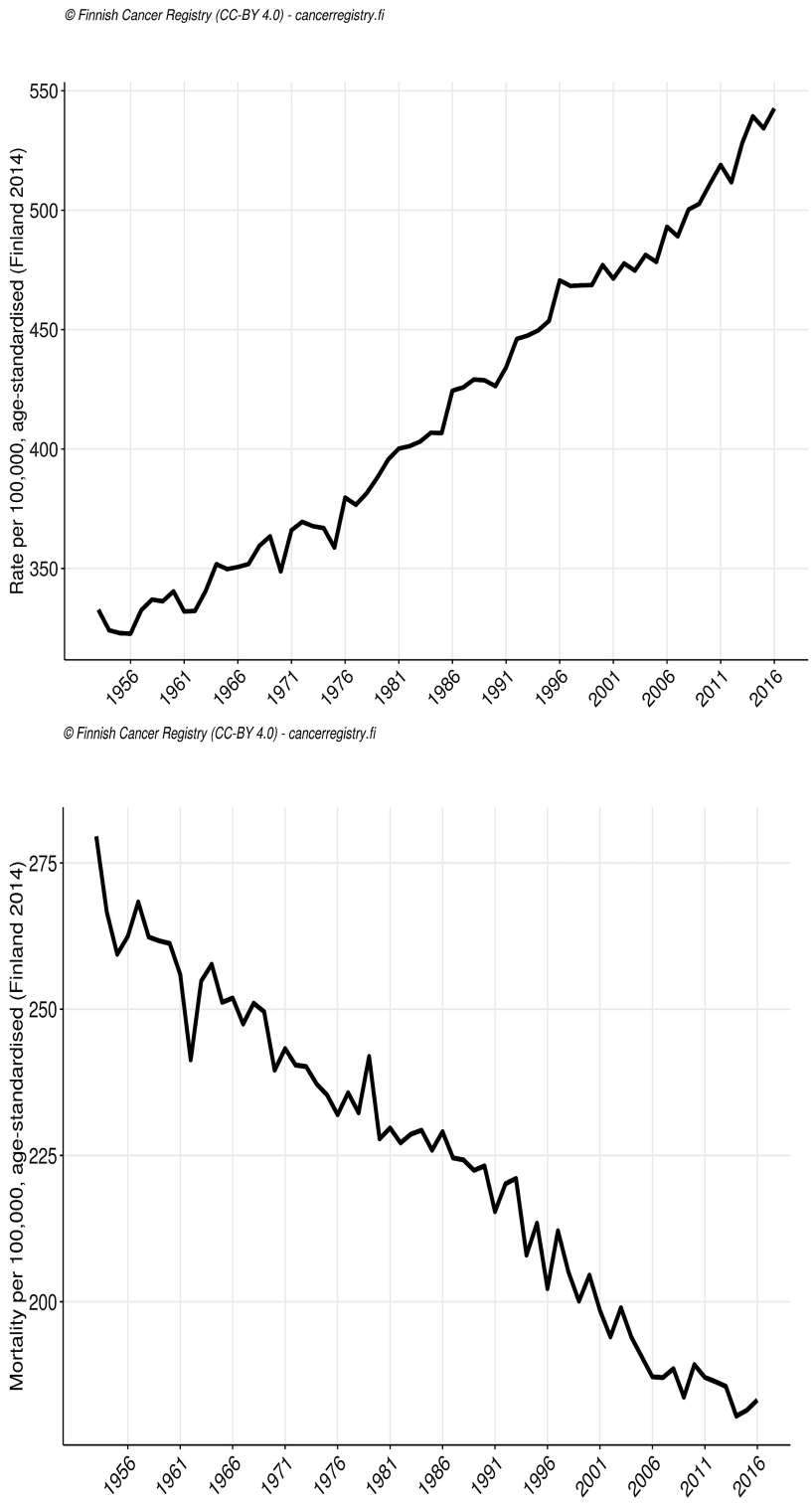


Figure 2. Top: New cancer cases diagnosed among Finnish women during 1953 to 2016, rate per 100,000, age standardized (Finland 2014). Bottom: Death due to cancer among Finnish women diagnosed between 1956 to 2016, mortality per 100,000, age standardized (Finland 2014). Source: Finnish cancer registry https://cancerregistry.fi.

2.2.2 Biology

The human breast (both female and male) contains mammary glands which are able to produce and eject milk. During puberty and pregnancy, female mammary glands undergo extensive postnatal development and expansion in response to stimulation by hormones such as estrogen, progesterone, and prolactin. The breast is composed of skin, hypodermis (fat and connective tissue with blood vessels and nerves), and breast tissue. The breast tissue is made up of epithelial parenchyma and the stromal elements. The milk production site of the breast consists of 15–20 lobes which further divide into 20–40 lobules composed of branched tubulo-alveolar glands. The lobes are connected by a ductal system which transports milk into the endpoint of the nipples. The lobules and ducts are lined with epithelial cells from which the majority of breast cancers arise. The size and perfusion of the mammary glands undergo extensive changes during thelarche, menstruation, pregnancy, lactation, menopause, and through aging. Under the stimuli of the pituitary and ovarian hormones, the breast tissue progressively develops and differentiates. The estrogen and progesterone receptor content of the breast impacts the proliferation activity, and therefore the risk of accumulation of DNA replication errors and cancer development. The proliferation activity is rapid especially between menarche and first childbirth, and declines with the terminal differentiation in the first full-term pregnancy (Li et al., 2008).

Whether or not a woman develops breast cancer is influenced by multiple factors including genetic predisposition and family history, history of mammary gland disease, age, hormones, early menarche, late child-bearing, age at menopause, and lifestyle. Women with one first-degree relative affected by breast cancer have a 1.8-fold higher risk of developing breast cancer compared to women who have no affected relatives. The risk increases to 2.93 and 3.9, respectively, for women with two and three or more first-degree relatives affected by breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 2001b). The likelihood of developing breast cancer increases through aging, which can be described, partly, by the accumulation of mutations. Further, breast tissue exposure to endogenous levels of estrogen and progesterone throughout reproductive years, as well as factors related to hormone levels, can influence the risk of breast cancer. For instance, for every year younger at menarche, the breast cancer risk increases by a factor of 1.05, and for every year older at menopause it increases by a factor of 1.03 (Collaborative Group on Hormonal Factors in Breast Cancer, 2012). Also, giving birth when younger than 24 years old seems to decrease the lifetime risk of breast cancer by 7%; however, the pattern appears to reverse for first pregnancy after age 35. The protective pattern is exhibited for prolonged breastfeeding, that is, every 12 months of breastfeeding decreases the risk of developing neoplastic disease by 4.3% (Collaborative Group on Hormonal Factors in Breast Cancer, 2002). It has been suggested that long-term exposure to exogenous estrogen, mainly through oral contraceptives and post-menopausal hormone replacements, might increase the risk of breast cancer. Mammographic density may affect cancer risk. An overview of 42 studies suggested that women with 70% or higher density have a 4.64-fold higher risk of developing cancer compared with women with less than 5% density (McCormack & dos Santos Silva, 2006; Duffy et al., 2018). Additional relevant elements involve lifestyle factors such as smoking, alcohol consumption, excess body weight, and physical inactivity. Although environmental factors may not have the same effect on everyone due to genetic heterogeneity, strong observational breast cancer risk association makes weight control, exercise, and moderation of alcohol intake advisable (Howell et al., 2014). The abundance of the above-mentioned risk

factors indicates the multi-directionality of the concept and studies investigating it. Yet, in a considerable number of breast cancer patients no risk factor is found.

Breast cancer is a heterogeneous disease, both genetically and clinically. Increased understanding of the histological, molecular, and functional divergence and characteristics of the disease formulates the classification standards of the various subtypes which impact diagnosis, prognosis, and treatment approaches (Turashvili & Brogi, 2017). Based on the site of the disease and whether it spreads beyond where it initially developed, breast cancer lesions are classified as invasive (infiltrating), which break through the wall of ducts and lobules and invade the surrounding tissues; and *in situ* carcinomas, which are local. The *in situ* carcinomas are further sub-classified into histologic subtypes including ductal carcinomas *in situ* (DCIS), which are confined to the ducts; and lobular carcinomas *in situ* (LCIS), which are found in the lobular epithelia and are much less common than DCIS. The histomorphological criteria classify invasive breast carcinomas into invasive ductal carcinomas (IDC), which comprise about 80% of all infiltrating breast cancers; invasive lobular carcinomas (ILC), which account for nearly 5–10% of cases; and other less common subtypes including medullar, tubular, papillary, and mucinous carcinoma (Makki, 2015).

In active clinical practice, the most widespread classification of breast cancers is the tumor-node-metastasis (TNM) staging system, which is based on tumor size, the number and location of involved lymph nodes, and the presence or absence of distant metastasis (Benson et al., 2003). Another decision-making factor in breast cancer treatment includes the grading system which assesses tubule formation, nuclear pleomorphism, and mitotic counts to indicate the overall tumor differentiation status: grade I is well-differentiated; grade II is moderately differentiated; and grade III is poorly differentiated (Elston & Ellis, 1991). To increase the accuracy of clinical decisions, it became necessary to incorporate molecular markers into the classification system and develop measurable prognostic and predictive markers. A prognostic marker is a clinical or biological factor which associates with the period of disease-free or overall survival regardless of therapy. A predictive marker is any measurable factor which associates with response or lack of response to a specific treatment (Clark, 2008). The conventional clinical biomarkers of breast cancers include ER (estrogen receptor), PR (progesterone receptor), and HER2/ERBB2/neu (human epidermal growth factor receptor 2), which are evaluated by immunohistochemical methods and classify the disease into basic therapeutic categories. Breast cancer cells which test positive for expression of ER and/or PR are classified as ER– and/or PR-positive. The majority of ER-positive breast cancers are also PR-positive, and together they account for roughly 65–75% of all breast cancer diagnoses. HER2 positivity indicates the amplification and/or overexpression of *HER2*, commonly measured by immunohistochemistry, fluorescence *in situ* hybridization (FISH), or chromogenic *in situ* hybridization (CISH), and appear in almost 15–20% of primary breast cancers. Other clinically relevant breast cancer molecular markers include the immunohistochemical status of Ki67, a nuclear protein expressed in S, G1, G2, and M phases of the cell cycle but nonexistent in G0, which reflects the growth fraction of neoplastic cell population and thus is an index of high proliferation rate in primary tumors (Yerushalmi et al., 2010). Another clinical marker is the somatic mutation of *TP53* which is found in 20–35% of human breast cancers. When missense mutated, TP53 accumulates in the nucleus of malignant cells. The protein level can be assessed with immunohistochemical methods and might indicate the prognosis of the disease (Varna et al., 2011; Olivier et al., 2006; Abubakar et al., 2019).

Breast cancer tumors are also classified into further distinct intrinsic subtypes based on the presence or absence of ER/PR, overexpression of HER2, expression of cytokeratin (CK) 5/6 (index of basal cells), expression of CK8/18 (index of luminal cells), high level of Ki67, and TP53 mutation, and their gene expression profiling. The intrinsic subtypes of breast cancer based on their molecular classification and gene expression signature are as follows:

(1) Luminal A-like, which is defined by ER/PR positivity, HER2 negativity, low expression of Ki67, expression of luminal associated markers including CK8 and 18, and comprises about 50% of all invasive breast cancers. Luminal A-like cancers usually have a good prognosis and are typically of low grade. Their relapse rate is significantly lower than other subtypes and their treatment is mainly based on endocrine therapy (Masood, 2016; Perou et al., 2000; Coates et al., 2015).

(2) Luminal B-like, which is ER/PR-positive, mostly HER2-positive, shows higher level of Ki67 compared to luminal A, and accounts for about 20% of invasive breast cancers. Luminal B-like breast cancers present a more aggressive phenotype and are of higher grade. The prognosis is poorer than luminal A and there is a higher recurrence rate and lower survival rate after relapse compared to luminal A. Their response to endocrine therapy and chemotherapy is variable (Masood, 2016; Perou et al., 2000; Coates et al., 2015).

(3) HER2-positive, which strongly overexpresses *HER2* and is negative for ER/PR or expresses lower ER levels. The HER2 subgroup also expresses a high level of Ki67 and is frequently *TP53* mutated. The HER2-positive subtype accounts for 15% of all invasive breast cancer. HER2-positive cancers are more often of high grade and have lymph node metastasis, which implies poor prognosis, but they present the highest response to trastuzumab (Herceptin) therapy which significantly improves the prognosis (Masood, 2016; Perou et al., 2000; Coates et al., 2015; Albergaria et al., 2011).

(4) The basal-like tumors comprise 8–37% of all breast cancers which express genes characteristic of the outer or basally located epithelial layer of the mammary gland, such as cytokeratins 5, 14, and 17 and the epidermal growth factor receptor (EGFR/HER1) and frequent mutation of *TP53*. Tha basal-like tumors that do not express ER and PR and do not overexpress *HER2* are classified as triple negative breast cancer (TNBC). TNBCs are highly proliferative tumors which manifest high histological and nuclear grade and have a higher rate of metastasis (Masood, 2016; Cheang et al., 2015).

(5) The normal-like subtype resembles the normal breast profiling and, similar to luminal A tumors, are ER/PR-positive, HER2-negative, and low Ki67. They express adipose and other nonepithelial genes and have high basal-like and low luminal gene expression. They usually show poor outcomes (Perou et al., 2000; Sorlie et al., 2001).

It is important to clarify that the basal-like subtype, which is highly heterogeneous, is only used in research settings and not utilized in routine clinical practice (Yersal & Barutca, 2014; Cheang et al., 2015). While daily clinical pathology practice applies the histologic type and grade, and immunohistochemical status of ER/PR/HER2 to determine the subtypes and consequently, the patient-tailored treatment strategies, the clinical value of gene expression signature is yet to be established.

The breast cancer mortality rate has drastically decreased, largely owing to early detection of the disease through increased cancer awareness and advanced screening tests which include: mammography, which is an X-ray picture of the breast; magnetic resonance imaging (MRI), which produces high resolution pictures of the breast without the application of radiation; molecular breast imaging (MBI), which employs a radioactive tracer that lights up the cancer tissues in the breast; breast biopsy, which collects tissue samples to be analyzed by pathologists; immunohistochemistry assay, which uses antibodies to detect certain protein expression; and blood-based assays, which use breast biomarkers to detect cancer but due to its low sensitivity is only recommended in the metastatic settings.

2.2.3 Breast cancer treatment

2.2.3.1 Predictive factors

Despite the increasing rate of breast cancer incidence, early detection and advances in therapy have improved the patients' survival rates. The decline of breast cancer mortality is attributable to reliable and clinically applicable predictive factors, which aid in choosing the treatment that is most likely to benefit individuals, as well as the improved adjuvant therapies after initial surgery. ER is a strong predictive marker which is commonly used to select patients who would benefit from endocrine therapy. In addition to ER, the PR measurement is considered to improve prediction of endocrine therapy response. Another strong predictive factor of breast cancer treatment response is HER2, which identifies patients who benefit from anti-HER2 therapy (Cao et al., 2016). The impact of ER, PR, and HER2 and their relation to breast cancer treatment is further described in the following section. The Ki67 protein expression, which is an index of proliferation rate and a somewhat common prognostic factor, has also been discussed to provide prediction potentials for chemotherapy response (Dowsett, et al., 2011). Further, the germline mutations in *BRCA1* or *BRCA2* represent promising predictive factors for PARP inhibitors for cancer therapy. However, the decision of which treatment to use might also be influenced by additional factors such as the stage and HER2 status of the cancer, as well as the status of other homologous recombination genes (Ohmoto, et al. 2017; Robson, et al. 2017).

2.2.3.2 Treatment

Most breast cancer patients have surgery to remove localized cancer. After the sentinel lymph node biopsy, patients with confirmed positive status undergo the removal of lymph node during surgery. The Types of surgery include breast-conserving surgery, total mastectomy, and modified radical mastectomy. However, modified radical mastectomy is a historical standard of management, which is withheld in the present day and used only for select patients. Surgery, radiation therapy, and systemic treatment, comprise the main care plan currently applied to treat breast cancer patients.

Radiation therapy decreases the risk of recurrent breast cancer by 16% (19% *vs* 35%) and the risk of mortality due to breast cancer by 4% (21% *vs* 25%) (Buchholz, 2011). While radiation therapy improves patients' survival, there is also evidence of dose-driven late complications, including the risk of late cardiac toxicity (Darby et al., 2013).

Systemic treatment of breast cancer includes cytotoxic, hormonal, and immunotherapeutic agents which are administered in neoadjuvant (i.e. preoperative), adjuvant (i.e. postoperative), and metastatic settings. Breast cancer subtype and anatomic cancer stage determine the standard systemic therapy administered which, in combination with patient preference, make for the optimal therapy.

Adjuvant chemotherapy, mostly administered as a combination treatment, reduces the risk of recurrent disease in early-stage breast cancer (Blum et al., 2017). Primary chemotherapy consists of regimens that may include non-anthracycline (containing combinations such as cyclophosphamide, methotrexate, and 5-fluorouracil (CMF)); anthracycline (in combination with other agents such as 5-fluorouracil, and cyclophosphamide (FAC)), cyclophosphamide and 5-fluorouracil (CAF), and cyclophosphamide (AC); taxane-based therapy (such as paclitaxel and docetaxel); and anthracycline and taxane combinations. Chemotherapy decreases the 10 year risk of death due to breast cancer by between 7% and 33% (Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2012, 2018; Schmidt, 2014). However, the major challenges ahead in the field of cancer therapy include: toxicities including (but not restricted to) immunosuppression, asthenia (fatigue), edema (swelling), and myalgias (muscle aches) (Tao, Visvanathan & Wolff, 2015); and the multiple pathways of resistance involved, i.e. while the first line of chemotherapy in metastatic or advanced disease is usually efficient, the vast majority of patients inevitably develop drug resistance in subsequent treatments (Gonzalez-Angulo, Morales-Vasquez & Hortobagyi, 2007).

In addition to chemotherapy, two hallmark events have drastically increased the breast cancer survival rate. First was the identification of endocrine hormonal therapy for ER/PR-positive patients in the 1980s, and second was the approval of HER2-direct monoclonal antibodies (trastuzumab) in treating HER2-positive patients in the 1990s. Endocrine therapy is a central component of both adjuvant and metastatic treatment for ER-positive patients. The ER and PR content of breast cancer cells are highly correlated with patient responses to hormonal therapy. Categorically, the non-metastatic patients with ER and/or PR positivity and HER2 negativity, which comprise almost 70% of breast cancer cases, receive five (to 10) years of oral endocrine treatment as their primary systemic therapy. Common endocrine therapies include tamoxifen, an antiestrogen medication effective in both pre– and postmenopausal patients; and aromatase inhibitors, which are effective only in post-menopausal patients (Waks & Winer, 2019). While the absolute benefit of tamoxifen is proportionate to the risk attributed to a given tumor, overall, ER-positive patients who are treated with five years of adjuvant tamoxifen experience at least a one third reduction of the risk of 15-year mortality due to breast cancer (Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2011). Aromatase inhibitors appear to benefit patients' survival even more than tamoxifen; five years of aromatase decreases 10-year mortality due to breast cancer by approximately 15% compared with tamoxifen — thus, by about 40% (proportionally) compared with no hormonal treatment (Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2015). In endocrine therapy, similar to other cancer therapies, toxicity concerns may lead to suboptimal treatment. The common (>10%) toxicities associated with endocrine therapy include hot flashes, arthralgias or myalgias (BIG 1-98 Collaborative Group et al., 2009).

In some hormone receptor-positive patients, chemotherapy and endocrine therapy are administered sequentially to achieve the optimal treatment. However, the clinician's decision on if and when to

add chemotherapy is based on clinicopathological features (which are not sufficient to assess the chemosensitivity), and at times the two gene expression signature assays (Harris et al., 2016; Krop et al., 2017) which are recommended by the American Society of Clinical Oncology — but not universally accepted due to early stage data. Therefore, the therapy combination that works best for patients, especially in node-positive disease, is somewhat defined through trial and error, which challenges the principal of avoiding overtreatment and undertreatment of patients.

The discovery and FDA approval of HER2-targeted therapy in the 1990s has been one of the greatest advances in breast cancer treatment. All confirmed HER2-positive patients, unless clinically inappropriate, receive HER2-targeted therapy such as trastuzumab, lapatinib, pertuzumab, and T-DM1. HER2-targeted therapy, typically in conjunction with chemotherapy, has dramatically increased the disease-free survival and overall survival rate of HER2-positive patients (Fisher et al., 1989; Slamon et al., 2001). Further, it has been shown that adding one year of trastuzumab to standard adjuvant chemotherapy, particularly docetaxel and carboplatin, increases disease-free survival and overall survival in patients with HER2 positivity (Slamon et al., 2011). The most notable, but not the most common, therapy complication associated with trastuzumab includes cardiotoxicity (Mohan et al., 2018). Ongoing investigations aim to reduce the duration of treatment and decrease the number of accompanying chemotherapy agents in lower risk patients in order to limit toxicities, as well as to discover novel agents to treat higher risk patients more effectively.

Perhaps the most challenging class of breast cancer to treat is the triple negative subtype, which has an aggressive clinical course and, due to the lack of established targeted therapy, virtually all triple negative patients receive chemotherapy. The 2017 result of the CREATE-X trial favored the administration of post-neoadjuvant fluorouracil-based drug capecitabine to improve patients' five-year disease-free survival by about 7%. However, due to early stage data and non-negligible toxicities, the integration of capecitabin into clinical treatment requires further examination (Masuda et al., 2017). Also, it has been suggested that adding carboplatin to a neoadjuvant chemotherapy regimen might marginally improve patients' disease-free survival in addition to an improved pathologic complete response at surgery (Masuda et al., 2017; Loibl et al., 2018). However, the role of a platinum-based agent in treating triple negative patients remains to be evaluated. One of the most promising therapeutic agents for breast cancer with *BRCA1* and *BRCA2* mutation or other homologous recombination deficiency is the PARP inhibitor, which functions based on the fact that PARP inhibition is lethal for BRCA1/2 deficient cells (Keung, Wu & Vadgama, 2019).

Finally, while the principles of systemic therapy are the same for both non-metastatic and metastatic patients, the therapeutic goals and extent of therapy might be slightly different between the two groups. Generally, in non-metastatic patients the aim of therapy is to eliminate tumor from the breast and surrounding lymph nodes, eradicate possible systemic spread of the disease and prevent metastatic recurrence, whereas in metastatic patients, the goal is to prolong life and alleviate symptoms (Waks & Winer, 2019).

While advances in diagnosis and treatment of breast cancer have decreased the mortality rate in high-income countries, patients in low-income countries bear a higher burden of cancer death and the difference is especially pronounced in women with younger age of onset (Bellanger et al., 2018). Therefore, to reduce breast cancer mortality worldwide, it is important to secure the

availability of early stage diagnostic methods to detect the cancer at a surgically removable stage, and to ensure patients' access to effective adjuvant treatment.

2.3 Genetic predisposition to breast cancer

Similar to most cancers, the majority of breast cancer cases arise from somatic mutation and thus are sporadic. However, family aggregation and epidemiological evidence indicate the role of hereditary factors in breast cancer development. The heritable component accounts for approximately 10% of all breast cancer (Easton, 2002). Population-based case control studies report that a family history of breast cancer and early age of onset (<40 years old) associate with increased risk of developing breast cancer. The 1.4-fold relative risk of women older than 60 years with a breast cancer relative diagnosed after age of 60 increases to five-fold relative risk in women younger than 40 years with breast cancer relatives diagnosed before age of 40 (Easton, 2002). The proportion also increases with the number of affected relatives, i.e. compared to women with no breast cancer family history, the reported risk ratio associated with one, two, and three or more affected relatives is 1.8, 2.93, and 3.9, respectively (Collaborative Group on Hormonal Factors in Breast Cancer, 2001a). In principal, observed family aggregation of breast cancer could arise from both genetic and non-genetic components, given that family members probably share a somewhat similar environment, but the discovery of BRCA1/2 germline mutations and twin studies indicate the impact of hereditary factors to be substantial (Michailidou et al., 2013; Lichtenstein et al., 2000).

Breast cancer in males is rare, accounting for less than 1% of all breast cancer cases. Overall, the lifetime risk of breast cancer in men is 1:1000 compared to 1:8 for women. However, the risk is increased two-fold for men with a first-degree breast cancer relative, indicating that the impact of heritable components is significant (Giordano, 2018).

Historically, in pursuit of breast cancer susceptibility genes, investigators applied three main methods: linkage analysis, screening of candidate genes, and genome-wide analysis study. Each method is best suited to discover a certain class of breast cancer susceptibility variants — that is high–, moderate–, and low-penetrance susceptibility variations, respectively — based on their allele frequency and penetrance. In general, the susceptibility alleles conferring lifetime breast cancer risk of >50%, >20% and >10% are broadly categorized as high–, moderate–, and low-penetrance predisposing variations (Ghoussaini, Pharoah & Easton, 2013). There is an adverse correlation between the allele frequency of the cancer predisposing variants and their penetrance, i.e., the high-penetrance cancer susceptibility variants have lower allele frequency in general population (Figure 3). The correlation is intuitively apparent, as the strong inherited predisposition to cancer is not present in the majority of individuals in general population.

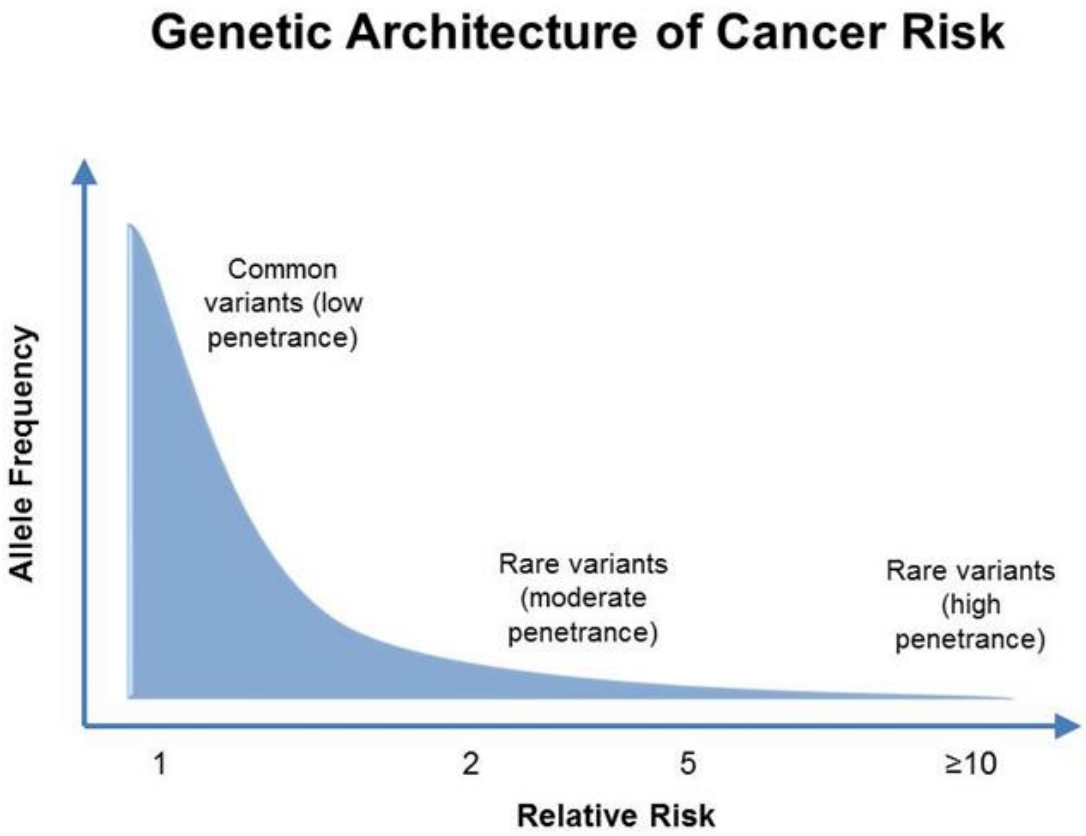


Figure 3. Source: National Cancer Institute: The general findings indicate the adverse association between the allele frequency and the penetrance of cancer predisposing variants.

High-risk families with breast cancer are typified by multiple cases with early onset (<50 years old), high rate of bilateral breast tumors, ovarian cancer, and the presence of male breast cancer cases. Nonetheless, one of the major difficulties in discovering germline cancer variants is that it can be challenging to unambiguously define the familial breast cancer cases. The reasons include the high breast cancer incidence rate in general population and the fact that sporadic breast cancer, too, can present as bilateral and occur prior to menopause. Therefore, rigorous methods of epidemiology and genetic analysis are essential for unfolding the hereditary basis of breast cancer.

2.3.1 High-penetrance breast cancer susceptibility genes

Using pedigree-segregating data, breast cancer studies applied linkage analysis to discover the high-risk breast cancer predisposing genes. *BRCA1* and *BRCA2* are the most important high-penetrance breast cancer genes. Additionally, mutations in high-risk cancer genes such as *TP53*, *PTEN*, *STK11*/*LKB1*, *CDH1* and *NF1* result in pleiotropic tumor syndromes including the cancerous

tumor(s) of the breast. The following subsections briefly discuss the high-risk breast cancer genes involved in hereditary cancer predisposition.

2.3.1.1 *BRCA1* and *BRCA2*

In 1990, Mary-Claire King and her colleagues established linkage of early onset familial breast cancer cases to the long arm of chromosome 17 (Hall et al., 1990), which by 1994, led to the mapping and cloning of *BRCA1* and the identification of *BRCA1* truncating mutations in families with multiple breast cancer cases (Miki et al., 1994). The *BRCA1* discovery was followed by mapping and positional cloning of the second breast cancer susceptibility gene, *BRCA2*, in 1995 (Wooster et al., 1995). BRCA1 and BRCA2 are caretaker tumor suppressors involved in DNA repair mainly by activating the repair of double-strand breaks and initiating homologous recombination DNA repair. *BRCA1/2* mutations are evenly distributed along the coding sequence of the genes. The germline mutations in *BRCA1/2* are often truncations of the open reading frame caused by small insertions and deletions, nonsense mutations, and splice site alterations. BRCA1/2 deficiency increases the genome instability and hypersensitivity to crosslinking events and agents, which produce double-strand breaks, and therefore, confer increased risk of cancer development.

Women carrying *BRCA1* or *BRCA2* mutations have a 57–65% or 45–55% risk for breast cancer by age 70, and a 39–44% or 11–18% lifetime risk of developing ovarian cancer, respectively (Antoniou et al., 2003, Chen, Parmigiani, 2007, Mavaddat et al., 2013). However, the pattern of cancer, as well as the estimated risk and prevalence conferred by *BRCA1/2* mutations, can vary between families, sample sets, and populations, possibly due to other modifying genes and components of family history, sample selection, and the environment. *BRCA1/2* mutations also increase the risk of developing Fallopian tube, colon, melanoma, and pancreas cancer (van der Groep, van der Wall & van Diest, 2011a). Men with mutations in *BRCA1* and *BRCA2* are at increased risk of developing breast cancer by 1.2% and 6.8%, respectively (Tai et al., 2007). *BRCA1* mutations account for 0–4% and *BRCA2* mutations account for 4–16% of all male breast cancer cases (Giordano, 2018). *BRCA1* and, particularly, *BRCA2* mutations in men also increase the risk of prostate cancer (van der Groep, van der Wall & van Diest, 2011b). However, about one third of male breast cancer cases without a known *BRCA1/2* mutation have a relative (male or female) with breast cancer, suggesting the possible involvement of additional genetic factors.

BRCA1/2-related breast cancer distribution of histopathological characteristics differs from that of other breast cancers. Both *BRCA1*– and *BRCA2*-related breast cancers are usually of high grade, but *BRCA1*-related tumors are more often grade 3 than *BRCA2*-related tumors. *BRCA1* cancers are usually triple negative basal-like subtypes, whereas *BRCA2* cancers are commonly hormone receptor positive. Also, *BRCA1* mutations often associate with medullary breast cancer tumors (Spurdle et al., 2014). Despite featuring the tumor characteristics associated with poor prognosis, studies do not provide conclusive results for poorer survival of *BRCA1/2* carriers compared to non-carriers (van den Broek et al., 2015), partially due to the relatively small sample size of the studies (because similar to other high-penetrance cancer genes, *BRCA1/2* mutations are rare in general population). *BRCA1* and *BRCA2* mutation frequency in general breast cancer patients unselected for family history, age of onset or other hallmarks of high-risk groups are as low as 0–7% and 1.1–

2.6%, respectively (Fackenthal & Olopade, 2007). An exception to the low frequency of *BRCA1/2* mutations in general population is the Ashkenazi Jewish population, in which the three main *BRCA*-founder mutations are very common (van der Groep, van der Wall & van Diest, 2011b).

2.3.1.2 Cancer predisposition syndromes

Some hereditary breast cancers are caused by other rare dominant autosomal hereditary syndromes such as Li-Fraumeni syndrome, Cowden syndrome and Peutz-Jeghers syndrome, which are associated with mutations in *TP53*, *PTEN* (phosphatase and tensin homolog), and SKT11/*LKB1* (liver kinase B1), respectively.

Li-Fraumeni syndrome is typified by familial clustering of early onset bone or soft tissue sarcomas, leukemias, and by increased risk of other carcinomas including those of the breast. *TP53* germline mutations are present in nearly 70% of families meeting the diagnostic criteria of Li-Fraumeni syndrome. The majority of mutations are missense, causing the synthesis of an abnormal TP53 mutant protein and subsequently the TP53 dominant negative effect (Malkin et al., 1990). The cumulative cancer risk in individuals carrying germline *TP53* mutation is high, with nearly 100% penetrance over carriers' lifetimes, and with females aged over 20 years having a higher risk than males due to breast cancer. Breast cancer accounts for 26.4% of all cancer diagnosis within Li-Fraumeni families, with 58% of them occurring before age 50; however Li-Fraumeni syndrome accounts for less than 1% of all breast cancer cases (Wooster & Weber, 2003). Female carriers have a 54% cumulative risk of breast cancer by age 70 (Mai et al., 2016; Amadou, Waddington Achatz & Hainaut, 2018). The role of *TP53* mutation in breast cancer will be further discussed in section 2.5.

Cowden syndrome, also known as multiple hamartoma syndrome, is another rare autosomal dominant hereditary cancer syndrome with an increased risk of breast cancer (Hobert & Eng, 2009). In addition to hamartomatous polyposis, Cowden syndrome also associates with pathognomonic physical features such as macrocephaly, delayed development, and oral papillomatous papules (Eng, 2000). Cowden syndrome is caused by a germline inactivating mutation in PTEN, which functions as a gatekeeper tumor suppressor through cell cycle arrest or apoptosis — or both — and plays a key role in inhibition of the oncogenic AKT/PI3K signaling pathway. Germline *PTEN* mutations also increase the risk of melanoma, thyroid, endometrium, colorectum and kidney cancers (Tan et al., 2012). Cowden syndrome female patients bear an elevated lifetime risk of developing breast cancer by 25–50% (Thull & Vogel, 2004) and an even higher risk (85%) was estimated in another study (Tan et al., 2012). Breast cancer in Cowden syndrome patients occurs in young age, starting at 30 years and commonly found between ages 38 and 46 (Hobert & Eng, 2009). Male breast cancer has also been suggested to associate with Cowden syndrome (Fackenthal et al., 2001).

Another rare autosomal dominant hamartomatous condition that significantly elevates the risk of breast cancer is Peutz-Jeghers syndrome. This syndrome is characterized by the development of benign hamartomas along the gastrointestinal tract and pigmented macules on the lips, fingers, toes and oral mucosae (Hemminki et al., 1998; Beggs et al., 2010; de Leng et al., 2007). Germline mutations in the *STK11*/*LKB1* gene are detected in 80–94% of affected families. STK11/LKB1 is a

tumor suppressor gatekeeper which is involved in cell cycle regulation. Patients with Peutz-Jegher syndrome are at an elevated risk of developing gastrointestinal and various non-gastrointestinal malignancies. The most commonly reported malignancies are colorectal cancer with a lifetime risk of 39%, followed by breast cancer with a risk of 31–54% by age 64 (Hearle et al., 2006; Giardiello et al., 2000).

CDH1 (cadherin-1) gene is another rare high-risk cancer gene in which the germline mutation also associated with elevated risk of hereditary lobular breast cancer. *CDH1* encodes for the E-cadherin protein, which is a transmembrane glycoprotein expressed in epithelial tissues and is involved in cell-to-cell adhesion and functions as a cell invasion suppressor. Aberrant E-cadherin compromises cell adhesion and increases cell motility and metastatic ability of the tumors (Corso et al., 2016). Mutations in *CDH1* associate with familial diffuse gastric cancer, an autosomal dominant cancer syndrome, and predispose affected females to lobular breast carcinoma. For *CDH1* mutation carriers, the risk of developing lobular breast cancer is 42% by age 80 (Hansford et al., 2015).

Germline alteration in *NF1* (neurofibromin 1) causes neurofibromatosis, which is characterized by multiple benign lesions. Patients affected by neurofibromatosis develop cancer at an elevated risk compared to the general population. Compared to other autosomal dominant malignancies discussed here, neurofibromatosis is the most common with a prevalence of 1/3500 (Frayling et al., 2019). Suggestive evidence indicates that women with neurofibromatosis have a five-fold increased risk of breast cancer manifested with more advanced forms of the disease (Suarez-Kelly et al., 2019; Easton et al., 2015).

2.3.2 Moderate-penetrance breast cancer susceptibility genes

Breast cancer investigators have identified moderate-risk genes mainly through resequencing of candidate genes. Also, recent developments in exome and whole genome sequencing have reduced, at least, the technical limitation of candidate gene studies and contributed to establishing novel moderate-risk breast cancer genes. Genes such as *PALB2*, *CHEK2* and *ATM* are among the well-studied moderate-penetrance breast cancer susceptibility genes.

PALB2 (partner and localizer of BRCA2), also known as *FANCN*, is a BRCA2 interacting factor and a linker protein between BRCA1 and BRCA2 (Xia et al., 2006), which plays a key role in DNA damage response through homologous recombination and the Fanconi anemia pathway (Nepomuceno et al., 2017). Bi-allelic germline loss-of-function in *PALB2* accounts for a subset of Fanconi anemia cases, whereas monoallelic loss-of-function contributes to increased breast cancer risk. Studies report that *PALB2* c.1592delT, a frameshift founder mutation in Finland which is present in almost 1% of breast cancer women unselected for familial history, confers a nearly six-fold increased risk of breast cancer; possibly this is due to compromising its BRCA2-binding capacity (Erkko et al., 2007). The absolute breast cancer risk for *PALB2* mutation carriers by 70 years of age and with no familial history is 33%, compared to the absolute risk of 58% in carriers with two or more first-degree breast cancer relatives at 50 years of age (Antoniou et al., 2014). Studies also suggest that *PALB2* mutations may increase the risk of male breast cancer (Antoniou et al., 2014; Blanco et al., 2012).

CHEK2 (checkpoint kinase 2) encodes for a serine/threonine kinase which has a key role in DNA repair, cell cycle regulation, and apoptosis in response to DNA damage. CHEK2 is activated through the phosphorylation of the Thr68 site by ATM (following DNA damage) or PRKDC (during normal mitosis) leading to its interaction with downstream substrates of apoptosis (including TP53 MDM2), DNA repair (including BRCA1 and PML), and components of mitotic spindle assembly (including BRCA1) (Magni et al., 2014; Kastan, & Bartek, 2004; Shang et al., 2014). A truncating mutation *CHEK2* c.1100delC associates with elevated risk of breast cancer. The estimate is slightly elevated for carriers with history of familial breast cancer (Schmidt et al., 2016; Nevanlinna & Bartek, 2006): a meta-analysis of 42 studies reported the aggregated odds ratio of 2.7 for unselected breast cancer versus the odds ratio of 4.8 for familial cases (Weischer et al., 2008). Another study summarized the estimated risk for carriers with no affected relative to be 20%, and for carriers with familial history to be 44% (Apostolou & Papasotiriou, 2017). An investigation of *CHEK2* c.1100delC in over 86,000 individuals in Copenhagen general population showed association also with other cancers, including those of the stomach, kidney, sarcoma and prostate (Naslund-Koch, Nordestgaard & Bojesen, 2016).

The *ATM* (ataxia telangiectasia mutated) gene encodes for a checkpoint kinase which is involved in the initiation of double-strand break repair through homologous recombination. Bi-allelic mutation of *ATM* associates with the rare autosomal recessive condition known as ataxia telangiectasia (AT) (Savitsky et al., 1995). AT is characterized by cerebellar ataxia, immunodeficiency, and elevated risk of cancer, especially leukemia and lymphoma. The heterozygous mutation of ATM does not cause AT but the carriers have a two– to three-fold elevated risk of developing breast cancer (Renwick et al., 2006; Thompson et al., 2005). This is an increased lifetime relative risk of 25% compared to the general population (Jerzak, Mancuso & Eisen, 2018).

Studies have suggested several other genes which are highly involved in homologous recombination repair of double-strand breaks as moderate-penetrance. The most notable genes include *BRIP1*, *RAD51C* and *RAD51D,* which mainly associate with ovarian cancer but may also impact breast cancer risk; however, their precise contribution to increased risk of breast cancer remains to be further investigated (Weber-Lassalle et al., 2018; Norquist et al., 2016; Pelttari et al., 2011). A series of other DNA repair genes — namely, *NBN* (Zhang et al., 2013), *MRE11A* (Bartkova et al., 2008), *XRCC2* (Park et al., 2012), *FANCM* (Kiiski et al., 2014), and *FANCC* (Thompson et al., 2012) — have been proposed to associate with breast cancer risk, however, the exact penetrance attributable to these genes is yet to be established (Easton et al., 2015). Table 1 summarizes the high– and moderate-risk cancer predisposing genes discussed here.

Table 1. High– and moderate-penetrance breast cancer predisposition genes and the predominant cancer susceptibility.

Gene	Cancer syndrome	Cancer	Estimated penetrance
BRCA1	Familial breast and ovarian cancer	Breast, Ovarian	55-65% breast, 40% ovarian
BRCA2	Familial breast cancer	Breast	45% breast, <20% ovarian
TP53	Li-Fraumeni syndrome	Breast, Sarcoma	90% (breast, females)
PTEN	Cowden syndrome	Breast, Thyroid, Endometrial	85% (breast)
STK11/LKB1	Peutz-Jegher syndrome	Breast	31-54% (breast)
CDH1	Familial diffuse gastric cancer	Breast, Gastric	42% (breast)
NF1	Neurofibromatosis type 1	Brain, Neural tumors, Breast	>95% develop benign lesions, 5% develop cancer
PALB2	Fanconi anemia	Breast	33-58%
CHEK2	Checkpoint kinase 2	Breast, Stomach	20-44% (breast)
ATM	Ataxia telangiectasia	Breast, Lymphoma	25% (breast)

2.3.3 Low-penetrance breast cancer susceptibility genes

Rare germline mutations in known high– and moderate-penetrance genes explain only 25% of familial risk and less than 5% of all breast cancer predisposition (Thompson & Easton, 2004). Family members usually share a similar environment, but the environmental factor is unlikely to explain all familial clustering of the disease. It is possible that it is partially attributable to the combination of common variants, each conferring a small breast cancer risk (Ghoussaini, Pharoah & Easton, 2013). Furthermore, twin studies have shown that the concordance for cancer is higher in monozygotic twins compared to dizygotic twins. For instance, one of the largest twin studies estimated a 5.2 relative risk of breast cancer for monozygotic twins compared to 2.8 in dizygotic twins (Lichtenstein et al., 2000). The higher cancer risk in monozygotic twins not only suggests that the genetic factor might be more important than the environmental factor, but also supports the hypothesis of breast cancer being a polygenic disease. Thus, the higher risk in monozygotic twins and the familial aggregation of breast cancer could also conceivably result from the cumulative impact of multiple low-penetrance alleles (Antoniou & Easton, 2006).

GWAS (genome-wide association studies) have identified the majority of low-risk common variants in breast cancer. The GWAS method is based on a tagging approach which scans markers, i.e. SNPs (single-nucleotide polymorphism) or CNVs (copy number variation), across the genome which are in linkage disequilibrium with each other. Owing to the linkage disequilibrium structure, the tagging SNPs represent similar information and impact as SNPs in the same haplotype block. However, this also means that the representative SNP may not necessarily be the causal variant. Detecting the causal variant is the most challenging part of GWAS, especially when the tagging SNPs reside in gene deserts. The identification and estimation of the causative variant is usually approached with methods of fine-mapping of the risk locus, phenotype prediction, heritability estimation, and functional annotation of pathway analysis (Easton et al., 2007). Many of these

variants are likely to play the regulatory role by modulating the expression of target genes (Michailidou et al., 2017). The power to discover common predisposing small size-effect variants largely depends on the sample size of both discovery population and the validation sets, which became possible through international consortia such as BCAC (Breast Cancer Association Consortium) (Broeks et al., 2011). Overall, common predisposing variants discovered by GWAS account for 18% of breast cancer genetic background (Michailidou et al., 2017). While individual susceptibility SNPs discovered by GWAS confer only a small risk, the combined effect as a polygenic risk score (PRS) is significant (Mavaddat et al., 2015).

Because of the small size effect, the predictive competence of low-risk SNPs for individuals is limited. However, an examination of population-based breast cancer cases to evaluate the potential of breast cancer risk prediction through common variants suggested that the power of common risk variables is useful for distinguishing between high– and low-risk groups (Pharoah et al., 2002, 2008). A study of 33,673 cases and 33,382 control women of European origin estimated the risk stratification ability of PRS of 77 breast cancer-associated SNPs: the study found that women in the highest and lowest 1% of the PRS bear a 29% and 3.5% risk of developing breast cancer by age 80 (Mavaddat et al., 2015) compared to women in the middle quantile (40^{th} to 60^{th} percentile). A recent large-scale case control study by the same researchers found that for the breast cancer PRS based on 313 SNPs, the lifetime risk of breast cancer among women in the highest 1% of the distribution is four-fold greater than those in the middle quantile. They also attempted to optimize PRSs for subtype-specific disease, and reported that women in the highest 1% of risk had 4.37– and 2.78-fold risks, and those in the lowest 1% of risk had 0.16– and 0.27-fold risks of ER-positive and ER-negative breast cancer, respectively, compared to women in the middle quantile. Interestingly, the predictive performance of the 313-SNP PRS significantly improved over their previous report of 77-SNP PRS, suggesting that the PRS based on low-risk SNP may offer powerful risk discrimination. However, the optimal assessment of risk discrimination requires the combination of PRS with family history, genetics, age, and other established risk factors (Mavaddat et al., 2019).

2.4 Genetics of breast cancer survival

Several factors — including, age, tumor stage, tumor subtype, drug sensitivity, and metastasis — may affect the likelihood of survival and indicated treatment in breast cancer patients (Goldhirsch et al., 2001; Pritchard et al., 2006). The TNM staging of the tumor strongly predicts breast cancer prognosis. Additionally, germline alterations might influence the age of onset, efficacy of adjuvant treatment, and the risk of certain tumor subtypes that are associated with the prognosis of the disease. Several studies investigated the association of the inherited component in characteristics and prognosis of breast cancer, and the molecular mechanism behind it.

Large Swedish population-based studies indicated that good and bad prognosis in breast cancer aggregate within families, which suggests the existence of a familial factor in patients' survival (Hemminki et al., 2008; Lindstrom et al., 2007; Hartman et al., 2007; Verkooijen et al., 2012) which could be largely distinct from familial risk (Hemminki et al., 2008). A breast cancer cohort study including 2,787 mother–daughter pairs and 831 sister pairs reported that first-degree relatives of a patient with a poor prognosis had a 60% higher breast cancer death rate compared to those of a

patient with a good prognosis, with a hazard ratio of 1.6 for daughters and 1.8 for sisters (Hartman et al., 2007). Children of parents with poor survival showed an increased hazard ratio of 1.7 for breast cancer death compared to those with good parental survival (Lindstrom et al., 2007). An additional population-based cohort study by Lindstrom et al., which included 1,617 sister pairs (almost twice as many as the previous study) (Hartman et al., 2007), found a two– to three-fold increased hazard ratio, adjusted for tumor characteristics and treatment, for breast cancer death in younger sisters with poor older sister survival compared to those with good sister survival (Lindstrom et al., 2014).

Although *BRCA1/2* genes were implicated as risk factors, their high penetrance and major functional role in DNA damage response pathways made them usual suspects also for survival studies. Breast cancer patients diagnosed under 50 years of age with *BRCA1/2* mutation are prone to unfavorable outcomes (Schmidt et al., 2017). However, the results of accumulated individual studies investigating the effect of *BRCA1/2* on patients' survival have been inconclusive, but tend to point to a lack of large impact (van den Broek et al., 2015; Verkooijen et al., 2006). The prevalence of *BRCA1/2* mutations is low, which results in limited statistical power for detecting the magnitude of their prognostic effect (Lee et al., 2010). Yet in a meta-analysis of 13 breast cancer survival studies, *BRCA1* associated with poor overall survival (HR = 1.50, 95% CI = 1.11–2.04) compared to non-carriers, but *BRCA2* mutations did not influence the likelihood of survival (Zhong et al., 2015). Among other rare high– and moderate-risk breast cancer genes, germline mutation in *PTEN* (Heikkinen et al., 2011), *PALB2* (Heikkinen et al., 2009), and *CHEK2* (Weischer et al., 2012) appeared to affect breast cancer progression and patients' survival. However, similar to with *BRCA1/2*, the low frequency of mutations make survival analyses challenging.

Many individual studies have reported the association between common germline variations in candidate genes and breast cancer survival (Azzato et al., 2008; Fasching et al., 2008; Ambrosone et al., 2005), but there has been little success in conclusively replicating them. It is noteworthy that statistical power, particularly the number of death events, plays a critical role in survival analysis and limits the detection power to variations conferring higher hazard ratios which are not likely to exist after all. Thus, a GWAS-based survival analysis with a modest sample size is often unsuccessful in consistently detecting prognostic alleles (Azzato et al., 2010a, 2010b). Recently, few large meta-analyses, which pooled genotype data from multiple breast cancer GWAS in populations of European ancestry attempted to identify common variants associated with breast cancer-specific survival. Guo et al. discovered a novel locus (rs2059614 at 11q24.2) associating with poor survival in breast cancer patients with ER-negative tumors (HR = 1.95, 95% CI = 1.55–2.47) (Guo et al., 2015). Another study by Khan et al. discovered two new loci (rs992531 at 8p21.2 and rs7701292 at 5q21.3) which associated with decreased survival among ER-positive patients (HR = 1.85) and endocrine-treated patients (HR = 1.79), respectively. Additionally, they conducted an interaction analysis which implicated that the survival association of rs7701292 is treatment-specific and independent of conventional prognostic markers (per-allele $HR_{rs7701292:\ endocrine}$ 1.92) (Khan et al., 2017).

The impact of heritable components on treatment outcome is less understood. Several studies have shown that genetic variations may influence treatment efficacy, which consequently influence breast cancer survival after diagnosis (Fagerholm et al., 2008; Schroth et al., 2007; Seibold et al.,

2013). There are also reports on the implications of SNPs in predicting therapy-related toxicity (Palmirotta et al., 2018). Kiyotani et al. conducted a Japanese GWAS analysis on 462 ER-positive breast cancer patients, including 240 study subjects and two independent sets of 105 and 117 cases of validation sets. The study identified rs10509373 in *C10orf11* gene which associated with recurrence-free survival in patients receiving adjuvant tamoxifen therapy (Kiyotani et al., 2012). Moreover, a two-study GWAS analysis found locus 19q13.41 represented by rs8113308 to associate with 10-year breast cancer survival after endocrine therapy, and proposed that patients carrying rs8113308 rare allele may not benefit from adjuvant endocrine treatment (Khan et al., 2015). Two other SNPs, i.e. rs6500843 and rs11155012, were also reported to associate with breast cancer survival in patients treated with chemotherapy, with rs6500843 specifically interacting with chemotherapy independent of other conventional prognostic markers, and rs11155012 specifically associating with anthracycline treatment (Fagerholm et al., 2015). Also, a homozygous missense variant, rs1800566, in oxidative stress response gene *NQO1* predicts poor survival among breast cancer patients, particularly after anthracycline-based adjuvant chemotherapy (Fagerholm et al., 2008). The role of NQO1 protein expression in breast cancer prognosis will be further discussed in sections 2.7 and 5.3.

2.5 *TP53*

TP53 associates with almost every type of human cancer and is the first gene described as a breast cancer gene. The implication of *TP53* somatic mutation in mammary carcinogenesis is evidenced by its high frequency in breast cancer (Nik-Zainal et al., 2019). The germline mutation in *TP53*, as mentioned in subsection 2.3.1.2, causes Li-Fraumeni syndrome: a familial cancer disorder. Women carrying germline mutation in *TP53* have a very high risk, up to 90%, of developing breast cancer. The risk conferred by *TP53* germline mutation is even higher than *BRCA1* and *BRCA2* mutations, but it is much rarer in the population.

Several studies have shown germline mutation in patients with familial background that fulfill either Li-Fraumeni syndrome or Li-Fraumeni-like syndrome criteria (Gonzalez et al., 2009; Ruijs et al., 2010). Under broader criteria of the Li-Fraumeni phenotype, it has been reported that 14% of patients with pathogenic mutations in *TP53*, which exhibit minor allele frequency of germline mutation, carry *de novo* mutation, i.e. not found in the parents. The *de novo* pathogenic mutation appears to be a consequence of somatic mutation occurring in a gamete cell of one parent or in the fertilized egg during early stage of embryogenesis (Batalini et al., 2019). Moreover, not all germline *TP53* mutation carriers belong to the Li-Fraumeni/Li-Fraumeni-like families. Two population-based breast cancer studies reported germline mutation in *TP53* among women with early (<40-year) onset breast cancer (Lalloo et al., 2006, Mouchawar et al., 2010). Of the unselected breast cancer patients in Lalloo (2006) and Mouchawar (2010) studies, 2 out of 63 (3%) and 2 out of 52 (4%), respectively, had no family cancer that met the Li-Fraumeni criteria, suggesting that the significance of *TP53* germline mutation in early-onset breast cancer is larger than previously thought and it might be extended outside clinically defined Li-Fraumeni syndrome (Lalloo et al., 2006; Mouchawar et al., 2010).

Apart from breast cancer predisposition, germline *TP53* mutation may impact the prognosis of breast cancer and the treatment outcome. For instance, the R72P (arginine 72 proline)

polymorphism has been suggested to affect the survival of breast cancer patients (Tommiska et al., 2005; Schmidt et al., 2009). It appears that TP53Arg72 induces apoptosis more efficiently than TP53Pro72 (Bergamaschi et al., 2006). However, the precise effect of this variation on patients' survival and its magnitude remains uncertain; perhaps partially due to TP53's diverse and complex molecular activity as well as the use of different clinical endpoints to evaluate prognostic significance. In addition to patients' survival, the R72P polymorphism appears to associate with the pathologic outcome of chemotherapy as well (Xu et al., 2005; Toyama et al., 2007; Vazquez et al., 2008). This particular polymorphism was also reported to influence therapy in other cancer types, such as its association with the clinical response to cisplatin-based chemoradiotherapy for advanced head and neck cancer patients (Bergamaschi et al., 2003). Apart from SNP309 and R72P, only a few studies have investigated the association between germline variation in genes involved in the TP53 stress response network and patient survival and drug response. A candidate gene study was performed by Vazquez et al. on 187 genotyped SNPs that reside in 138 genes involved in mediating the TP53 stress response. The study found seven SNPs in five genes with significant genotype-drug response association *in vitro* by using data generated through the NCI anticancer drug screen (NCI60 screen). The strongest association was found for SNPs rs6734469 and rs187115 in *YWHAQ* and *CD44*, respectively (Vazquez et al., 2011). An interaction analysis between haplotype-based germline SNPs and TP53 tumor status identified one locus, represented by rs10916264, which associated with worse survival among patients with ER-positive and TP53-positive tumors, and another locus, represented by rs798755, which was speculated to associate with patient survival in interaction with anthracycline treatment (Fagerholm et al., 2017).

Unlike the association of *TP53* germline variation with prognosis and treatment outcomes, the effect of TP53 tumor status has been studied extensively (Aas et al., 1996; Bertheau et al., 2002, 2008) suggesting that TP53 mutant patients have poor overall survival compared to those with the wild-type TP53 tumors. The effect is also pronounced among patients with ER positivity, and HER2-enriched patients (Silwal-Pandit et al., 2014). While the functional p53 and its apoptotic activity are suggested to be essential for the initiation of response to genotoxic stress, such as cytotoxic chemotherapy, the predictive value of *TP53* status in breast cancer treatment response is rather inconclusive.

The *TP53* gene is a trans-regulatory element which resides at 17p13.1 and encodes for the TP53 tumor suppressor protein. TP53 protein regulates the growth inhibitory genes and its tumor suppressor role seems to be linked to its transcription factor function. The diverse gene transcripts regulated by TP53, also known as P53-dependent transcriptome, are mostly involved in pathways of cell survival and genome stability (Hafner et al., 2019). In the regulatory context, the TP53 level in normal condition is within a narrow range of intracellular concentration due to a highly regulated process involving the physical interaction of TP53 and the E3 ubiquitin ligase MDM2. The ubiquitination of TP53 by MDM2 leads to its continuous degradation which keeps it at low level. The phosphorylation of TP53 in response to DNA damage renders it insensitive to MDM2, resulting in its accumulation in the cell (Kubbutat, Jones & Vousden, 1997). On the other hand, TP53 itself transcriptionally activates MDM2 to form a regulatory feedback loop (Lahav et al., 2004). *MDM2* level is elevated in several cancer cells, including those of the breast (Shaikh et al., 2016). A common single nucleotide polymorphism (SNP309) in the first intron of *MDM2* within the promoter region impacts the binding site of a transcriptional activator, resulting in the enhanced

level of *MDM2* transcript. SNP309 has been suggested to associate with increased incidence of early-onset breast cancer (Wasielewski et al., 2007), however in a large study by BCAC, no such association was found (Schmidt et al., 2007). Although the *MDM2* SNP309 was suggested to predict poor survival in other cancers such as leukemia (Gryshchenko et al., 2008), it did not seem to predict breast cancer patients' survival (Toyama et al., 2007; Boersma et al., 2006). However, evidence of predisposition to worse breast cancer survival was observed for *MDM2* SNP309 in combination with TP53 R72P (Schmidt et al., 2009). The first study performed for this thesis investigated the breast cancer survival association of candidate *TP53* stress response network genes, as well as their interaction with *TP53* R72P and *MDM2* SNP309.

In the functional context, the TP53-dependent pathways include:

(1) cell cycle arrest: the TP53-dependent inactivation of pro-cell cycle cyclin-dependent kinases through CDKN1A (Engeland, 2018);

(2) apoptosis: the activation of a set of genes including BAX, PUMA, FDXR and CCNG1 that collectively destabilize mitochondria and decrease the threshold of programmed cell death;

(3) DNA repair: the DNA damage-triggered regulation of a set of genes involved in DNA repair pathways such as *XPC*, *GADD45* and *DDB2,* which together with genes participating in cell cycle arrest maintain the genome integrity of the cell (Fischer, 2017);

(4) metabolic checkpoint: in response to the enhancement of aerobic glycolysis to provide ATP and lactate (Warburg effect), TP53 negatively regulates the oncogenic metabolic adaption of cancer cells through the regulation of a set of genes, most notably *SCO2* (Zhang, Qin & Wang, 2010), or by initiating the AMPK-dependent cell cycle arrest/senescence in response to glucose deprivation (Jones et al., 2005);

(5) redox regulation: oxidative stress stimulates the DNA binding activity of certain transcription factors including NF-κB, AP-1, and NQO1; the latter of which induce cell cycle arrest and apoptosis to maintain the stability of the cell under hypoxia (Paranjpe & Srivenugopal, 2013).

Previous *in vitro* and *in silico* evidence (Vazquez et al., 2008, 2010, 2011) suggested the impact of TP53 network genes in cancer therapy. That — in addition to a study by Fagerholm et. al (2008) which suggested prognostic and predictive potentials for p53 status, along with NQO1, especially after anthracycline-based chemotherapy — prompted Study I of this thesis.

2.6 *NF-κB*

NF-κB (nuclear factor kappa B) is another transcription factor heavily involved in important biological processes including immune and inflammatory responses, survival, senescence, energy metabolism, and oxidative stress response. Similar to a number of diverse transcriptional factors, such as TP53 and STAT, NF-κB belongs to a class of proteins known as immunoglobulin-fold, which are not similar in their sequences but are structurally related (Rudolph & Gergen, 2001). The NF-κB transcription factor family consists of five members, namely RelA/p65, c-Rel, RelB, NF-

κB1 (p50), and NF-κB2 (p52) which generally function as homo- or heterodimers. In absence of pathway stimuli, the NF-κB members are bound to IκB (inhibitor of NF-κB), which keeps them transcriptionally inactive. Also, similar to TP53 and MDM2, there is a feedback regulatory loop between NF-κB and IκB. Upon activation the IκB is phosphorylated, leading to its detachment from NF-κB members and its proteasomal degradation. Then, the NF-κB dimers translocate to the nucleus to induce or suppress the expression of their target genes (Sethi, Sung & Aggarwal, 2008).

There are two main pathways (canonical and non-canonical) which lead to the activation of NF-κB. The main activating approach, i.e. detaching IκB from NF-κB dimer, as well as some intermediate signal transduction factors such as TRAF2, are common in both pathways. The two pathways differ mainly in the factors and molecular receptors — such as TNFR1/3 in canonical pathways versus BAFFR/TRAIL-R4 in non-canonical pathways — which trigger NF-κB activation. They also differ in the intermediate factors, including the IκB-targeting kinase complexes (IKK) as well as the downstream NF-κB members. The IKK complex in canonical pathways consists of IKKα and IKKβ kinases and the regulatory subunit IKKγ/NEMO, whereas in non-canonical pathways the NF-κB-inducing kinase (NIK) does not involve NEMO (Fusella et al., 2017; Hoesel & Schmid, 2013). Figure 4 briefly illustrates the two main pathways involved in NF-κB activation.

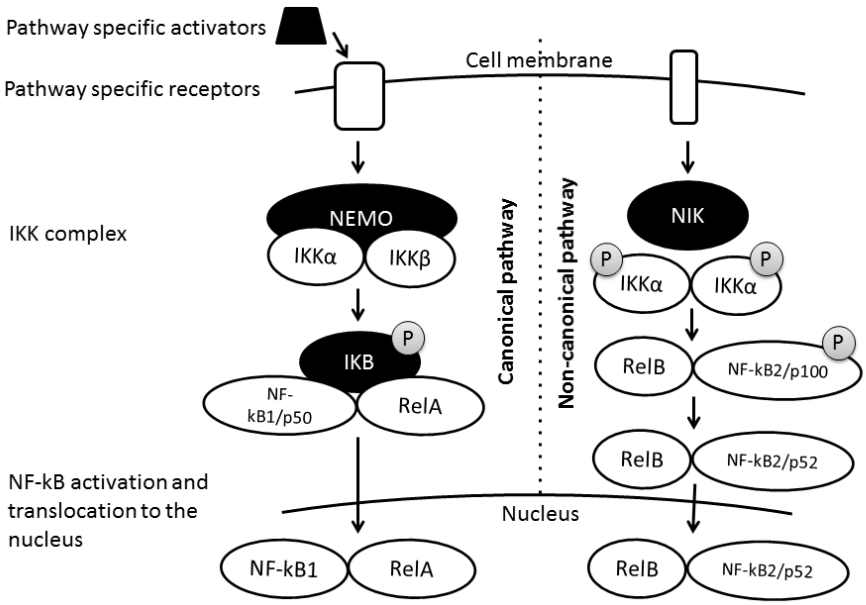


Figure 4. Canonical and non-canonical pathways involved in the activation of diverse NF-κB family members. In the canonical pathway, left pane, the pathway-specific signaling factors (e.g. TNFα) activate their specific receptors (e.g. TNFR) which lead into the kinase activity of the IKK complex and detachment of IκB from NF-κB dimer. The released NF-κB dimer then translocates into the nucleus for its subsequent transcriptional factor activities (Sethi, Sung & Aggarwal, 2008). In the non-canonical pathway, right pane, following the activation of receptors (e.g. BAFFR), NIK activates IKKα which lead into phosphorylation and proteasomal processing of P100 into P52-P52 which then, along with RelB, is translocated to the nucleus to function as a transcription factor.

Given the importance of biological processes influenced by NF-κB signaling pathways (such as inflammatory response, cell survival, energy metabolism, and oxidative stress response), its possible impact on cancer development and treatment efficacy is expected (Karin, 2006). Aberrant regulation of NF-κB pathways contribute to the tumorigenesis of breast cancer (Biswas et al., 2004; Boehm et al., 2007; Nakshatri et al., 1997). NF-κB level is elevated in breast cancer tumors (Cogswell et al., 2000) and appears to vary among subtypes especially depending on ER status. For instance, activated NF-κB is detected in ER-negative human breast cancer cells with overexpression of ErbB1 (Biswas et al., 2000, 2001, 2003), and the relative level of NF-κB inversely correlates with the expression of estrogen receptors, suggesting that they might mutually repress each other (Nakshatri et al., 1997; Gionet et al., 2009).

The association of single nucleotide polymorphism in the NF-κB pathway genes with breast cancer prognosis has been little studied so far (Kim, Hagemann & DeMichele, 2009; Murray et al., 2013). A breast cancer survival study on SNPs within or in the 100kb flanking region of genes involved in human immunology and inflammation suggested that rs4458204, linked to NF-κB-target chemokine ligand *CCL20*, influences breast cancer survival in patients with ER-negative tumors who have been treated with chemotherapy (Li et al., 2014). The impact of NF-κB on breast cancer treatment might be linked to its mutually repressing relationship with ER, or in a more general aspect, due to its elevated activity in cancer cells which induce a survival mechanism by up-regulating anti-apoptotic genes (Katsman, Umezawa & Bonavida, 2009), thereby providing a major causative environment for drug resistance. The second study performed for this thesis investigated the impact of NF-κB signaling pathways on breast cancer patients' survival and treatment outcome.

2.7 *NQO1*

NQO1 (NAD(P)H:quinone dehydrogenase 1) gene resides on 16q22.1 and encodes for NQO1 which is a multifunctional enzyme involved in cellular defense against cytotoxicity and carcinogenicity of quinones, especially under oxidative stress (Talalay & Dinkova-Kostova, 2004; Adikesavan, Barrios & Jaiswal, 2007). The cytotoxicity of quinones can arise through the hypoxia stress when their one electron is reduced leading to the production of a semi-quinone free radical which is attributed to DNA damage. By catalyzing the reduction of quinone to hydroquinone in a single two-electron step, NQO1 bypasses the production, and thus the toxicity, of semi-quinone free radicals. However, hydroquinone itself can be redox-labile and form cytotoxic reactive oxygen species DNA (Ross et al., 2000).

The reports on the impact of NQO1 on cancer development are controversial, perhaps due to its fundamental enzymatic activity which can diversely affect the molecular players of cellular environment, as well as its crosstalk with other important signaling pathways such as *TP53* and *NF-κB* (Thapa et al., 2014). It has been demonstrated that treating NQO1 wild-type cells with dicoumarol, an inhibitor of NQO1, abolishes TNF-induced NF-κB activation (Ahn et al., 2006; Iskander et al., 2006). NQO1 also regulates TP53 stability and the lack of NQO1 activity promotes TP53 degradation which inhibits apoptosis (Asher et al., 2002). It has been suggested that NQO1 also inhibits the degradation of $P33^{NG1b}$, a tumor suppressor protein downregulated in several

carcinomas (Garate, Wani & Li, 2010). Dysregulation of NQO1 has been found in several cancer types.

The most notable aberrant form of NQO1 is the null enzyme activity attributed to TT genotype of *NQO1* C609T (rs1800566) mutation, which was found in eight cancer types, including those of the breast (Hamajima et al., 2002). The same mutation was reported to strongly associate with poor survival among breast cancer patients, particularly after anthracycline-based adjuvant chemotherapy and in TP53-aberrant tumors (Fagerholm et al., 2008). The third study conducted for this thesis analyzed immunohistochemical staining of NQO1 and NF-κB, in two series of invasive breast cancer tumors, for their association with clinicopathological characteristics of the tumor as well as patients' survival.

2.8 *microRNAs*

MicroRNAs (miRNAs) are short (about 20–22 nucleotides) functional RNAs known as post-transcriptional regulators of gene expression by either degrading or translationally repressing their target mRNAs (Wilczynska & Bushell, 2015). Through the canonical miRNA biogenesis, the primary miRNA processor (pri-miRNA) is processed into precursor miRNA (pre-miRNA) followed by their transportation from nucleus to cytoplasm. The pre-miRNA are then cleaved by ribonuclease Dicer into miRNA duplex, but only one strand becomes mature miRNA and the other strand is degraded. Mature miRNAs are loaded into RISC (RNA-induced silencing complex) and bind to the complementary sequence of their target mRNAs, which result in translational inhibition and mRNA decay (Treiber, Treiber & Meister, 2019). The crosstalk between miRNAs and biologically essential signaling pathways, such as TP53 and NF-κB, may play a major role in activation or inhibition of pro-tumorigenesis cascade of transcriptional events (Jones & Lal, 2012; Ma et al., 2011).

There is increasing evidence of the impact of miRNAs on human cancer (Iorio & Croce, 2012). Several studies implicated the association of miRNAs and breast cancer pathogenesis and such miRNAs can be classified as oncomiRs (Li et al., 2012; Jiang et al., 2010), tumor suppressors (Feliciano et al., 2013), metastamiRs (pro-metastatic) (Huang et al., 2008), or metastasis suppressors (Tavazoie et al., 2008). Moreover, miRNAs are differentially expressed in breast cancer subtypes including basal versus luminal tumors (Blenkiron et al., 2007; Sempere et al., 2007), HER2-positive versus HER2-negative tumors, and ER-positive versus ER-negative tumors (Mattie et al., 2006; Lowery et al., 2009). Studies also suggest miRNAs as the predictors of breast cancer prognosis and treatment sensitivity, for instance: high-circulating (serum) level of miR-202 significantly correlated with reduced overall survival (Joosse et al., 2014); four-miRNA signature (miR-18b, miR-103, miR-107 and miR-652) in breast cancer patient serum associated with relapse-free and overall survival and can be a prognostic classifier of patients with TNBC (Kleivi Sahlberg et al., 2015); high level of miR-125b associates with poor response to Taxol treatment (paclitaxel) (Zhou et al., 2010); and high plasma miR-210 associated with poor sensitivity to trastuzumab (Jung et al., 2012).

Despite the frequent reports of miRNAs' contribution to cancer development, to establish the role of individual miRNA or group signatures these findings are required to survive the validation tests followed by functional studies.

2.8.1 miR-30 family

The miR-30 family consists of five members (i.e. miR-30a–e) encoded from three different genomic locations (miR-30c and miR-30e at 1p34.2; miR-30a at 6q13; and miR-30b and miR-30d at 8q24.22), with extremely high sequence homology and 100% conservation in the seed region (Kozomara & Griffiths-Jones, 2014). Several studies implicate the role of miR-30 family members in biological and pathological processes such as senescence (Martinez et al., 2011), apoptosis (Liu et al., 2016; Xia et al., 2010), and autophagy (Zhu et al., 2009). Also, multiple studies have reported the downregulation of miR-30 family members in multiple cancer types and metastatic disease, including breast (Zhang et al., 2014), lung (Kumarswamy et al., 2012), thyroid (Boufraqech et al., 2015), HCC (Liu, Tu & Liu, 2014), and gastric cancer (Sousa et al., 2016). However, in some cancers, miR-30 family members showed oncogenic features (Li et al., 2012; Gaziel-Sovran et al., 2011; Dobson et al., 2014). The diverse impact of miR-30 family members is not uncommon and is reported even in the well-studied miRNA families such as miR-200 (Elson-Schwab, Lorentzen & Marshall, 2010). In general, the differential behavior of miRNAs may be due to several reasons such as the variety of their targeting mRNAs, their involvement in diverse functional pathways, and the different types of tumors.

Accumulating studies report the impact of several miR-30 family members in breast cancer prognosis, metastasis, chemosensitivity, and treatment outcome. MiR-30a inhibits breast cancer proliferation and metastasis by directly targeting the metastasis gene metadherin (*MTDH*) (Zhang et al., 2014). Cheng et al. (2012) demonstrated the suppressive impact of miR-30a on another metastatic associated protein, vimentin, which resulted in reduced migration and invasiveness of breast cancer cells. Another recent study found that miR-30a is downregulated in TP53-inactivate TNBC and associates with reduced outcome (di Gennaro et al., 2019). A study by Bokhorn et al. (2013) showed that miR-30c inhibits the chemoresistance of breast tumor through its regulator effect on cytoskeleton genes TWF1 and IL-11 which are involved in cell motility, drug sensitivity and cancer progression. Higher expression of both miR-30a and miR-30c associates with better tamoxifen therapy and longer progression-free survival (Rodriguez-Gonzalez et al., 2011). The expression of another miR-30 family member, miR-30e*, appeared as a protective prognostic marker in the *ESR1+/ERBB2−* subtype of breast cancer (D'Aiuto et al., 2015). A study by Li et al. (2012) which suggested miR-30d as a significant modifier of patients' survival in ovarian cancer — i.e. an inverse association with patients' survival — prompted the investigation of miR-30d in breast cancer survival in Study IV. The fourth study performed for this thesis found association between miR-30 family members with breast cancer survival and treatment outcome.

3 Aims of the study

The objective of this thesis was to investigate key cancer-related pathways and regulatory elements to identify prognostic and predictive markers associating with breast cancer patient survival and treatment outcome.

The studies performed for this thesis investigated:

- The impact of germline mutation in *TP53* regulatory network genes on breast cancer survival and treatment outcome.
- The association between SNPs in the NF-κB activating pathway and breast cancer survival.
- The associations of NQO1 protein expression and NF-κB nuclear localization with breast cancer survival and treatment outcome.
- The role of miR-30 family members on breast cancer survival and treatment outcome.

4 Material and method

4.1 Study subjects

4.1.1 Germline DNA samples and genotype information

The Breast Cancer Association Consortium (BCAC) is an international multidisciplinary consortium formed in April 2005, dedicated to breast cancer research. There are over 100 groups currently contributing to BCAC and providing information about their study subjects including genotyping, clinical, demographics, and key epidemiological data (http://bcac.ccge.medschl.cam.ac.uk/)(Breast Cancer Association Consortium, 2006, Broeks et al., 2011). Since the study members are from multiple ethnicities and were designed to benefit different scientific investigations, the eligible contributing studies in each BCAC collaborative project may be different.

In Study I (Jamshidi et al., 2013), genotypes of the selected SNPs in the TP53 regulatory network were obtained from germline DNA samples in four European studies within BCAC. Genotype data was available for altogether 4,701 invasive breast cases, namely the Amsterdam Breast Cancer Study (ABCS)(n=1,442), the Hannover Breast Cancer Study (HABCS) (n=794), the Helsinki Breast Cancer Study (HEBCS)(n=925), and the Polish Breast Cancer Study (PBCS)(n=1,540) (see Table 2 for detailed description). HEBCS-GWAS patients included in BCAC, and for whom samples were previously genotyped for a genome-wide case-control breast cancer risk study (Li et al., 2010, 2011), were used as the initial study population followed by further evaluation in the rest of the contributing studies and in the pooled dataset. The HEBCS (n=925) peripheral blood samples originated from the large Finnish breast cancer study population, which consists of two series of unselected breast cancer patients (n=1,870) and additional familial cases (n=540) ascertained at the Helsinki University Central Hospital. The unselected set consisted of two cohorts which were collected in 1997–1998 and 2000 (Kilpivaara et al., 2005; Eerola et al., 2000), and in 2001–2004 (Fagerholm et al., 2008), and cover 79% and 87% of all consecutive, newly diagnosed cases treated at the hospital at the time of collection, respectively. The additional familial cases were collected at Helsinki University Central Hospital, Department of Clinical Genetics, and BRCA1 and BRCA2 mutation cases had been excluded from the familial patient series (Eerola et al., 2000; Vehmanen et al., 1997). Of 925 HEBCS invasive breast cancers, 760 samples were from the unselected and familial breast cancer set which were genotyped with Illumina 550k SNP array and an additional 165 ER-negative samples were genotyped with the Quad610.v1 platform (Li et al., 2010, 2011). The *TP53* R72P (rs1042522) and *MDM2* SNP309 (rs2279744) were genotyped using the TaqMan assay (Schmidt et al., 2009). The *TP53* R72P was genotyped in PBCS as described previously (Garcia-Closas et al., 2007). The genotyping for the *PRKAG2* and *PPP2R2B* SNPs was also carried out using Applied Biosystems TaqMan SNP genotyping assays. Genotyping for *PRKAG2*-02 (rs4726050) in ABCS and *PRKAG2*-04 (rs7789699) in PBCS failed to produce high quality genotypes; for that reason, these particular results were not included in the analysis. A higher frequency of homozygous rare alleles and deviation from the Hardy–Weinberg equilibrium for *PPP2R2B* (rs10477313) was seen among ABCS samples, but the results for this SNP were in line with the rest of the studies (Jamshidi et al., 2013).

In Study II (Jamshidi et al., 2015), primary data from a total of 24 studies (n=30,431 invasive breast cancer cases of European ancestry) participating in BCAC were used (Table 2). To enter the analyses, each study was required to have a minimum number of 10 events (death). The germline genotype information of the SNPs were obtained from data available in an Illumina iSelect genotyping array (iCOGS) which was custom-designed for the Collaborative Oncological Gene-environment Study (COGS) (Michailidou et al., 2013).

Table 2. List of contributing studies

Thesis study	Participatin Study	Abbreviation	Country	Total Cases*	Age range	Study design	References
II	Australian Breast Cancer Family Study	ABCFS	Australia	1610	23 69	Population-based case-control study	Dite,G.S. 2003
I & II	Amsterdam Breast Cancer Study	ABCS	Netherlands	1716	23 50	Hospital-based consecutive cases; population-based controls	Schmidt,M.K. 2007
II	Bavarian Breast Cancer Cases and Controls	BBCC	Germany	1443	22 96	Hospital based cases; population based controls	Fasching,P.A. 2008; 654 Schrauder,M. 2008
II	Breast Cancer Study of the University of Heidelberg	BSUCH	Germany	1114	25 89	Hospital based cases;healthy blood donator controls	Breast Cancer Association Consortium 2006
II	Copenhagen General Population Study	CGPS	Denmark	3363	26 100	Population-based	Bojesen,S.E. 2005; 658 Weischer,M. 2007
II	ESTHER Breast Cancer Study	ESTHER	Germany	757	30 81	Population-based case-control study	Breast Cancer Association Consortium 2006
I	Hannover Breast Cancer Study	HABCS	Germany	794	25 91	Hospital-based case-control study	Dork,T. 2001
I & II	Helsinki Breast Cancer Study	HEBCS	Finland	2404	22 96	Hospital-based case-control study + additional familial cases	Syrjakoski 2000; 107 Kilpivaara 2005
II	Karolinska Breast Cancer Study	KARBAC	Sweden	832	24 88	Population and hospital-based cases; geographically matched controls	Lindblom,A. 1992; 661 Margolin,S. 2004
II	Kuopio Breast Cancer Project	KBCP	Finland	514	23 92	Population-based prospective clinical cohort	Hartikainen,J.M. 2005; 663 Hartikainen,J.M. 2006
II	Kathleen Cuningham Foundation Consortium for research into Familial Breast	KConFab/AOCS	Australia and New Zeland	631	19 78	Clinic-based recruitment of familial breast cancer patients (cases); population-based case-control study of ovarian cancer (controls only)	Mann,G.J. 2006; 665 Beesley,J. 2007
II	Leuven Multidisciplinary Breast Centre	LMBC	Belgium	2035	21 95	Hospital-based case-control study	De Maeyer,L. 2008; 667 Neven,P. 2008
II	Mammary Carcinoma Risk Factor Investigation	MARIE	Germany	3813 with questionnaire, 2768 with questionnaire +	50 74	Population-based case-control study	Flesch-Janys,D. 2008
II	Mayo Clinic Breast Cancer Study	MCBCS	USA	1807	22 89	Hospital-based case-control study	Olson,J.E. 2007
II	Melbourne Collaborative Cohort Study	MCCS	Australia	1234	30 82	Population-based prospective cohort study	Giles,G.G. 2002
II	Multi-ethnic Cohort	MEC	USA	873	46 82	Prospective cohort study: nested case-control	Kolonel,L.N. 2000
II	Oulu Breast Cancer Study	OBCS	Finland	544	28 92	Hospital-based case-control study	Breast Cancer Association Consortium 2006
II	Ontario Familial Breast Cancer Registry	OFBCR	Canada	1424	22 81	Population-based familial case-control study	John,E.M. 2004
II	Leiden University Medical Centre Breast Cancer Study	ORIGO	Netherlands	1456	22 88	Hospital-based prospective cohort study	de Bock,G.H. 2004; 674 Huijts,P.E. 2007
I & II	NCI Polish Breast Cancer Study	PBCS	Poland	2136	27 75	Population-based case-control study	Garcia-Closas,M. 2006
II	Karolinska Mammography Project for Risk Prediction of Breast Cancer - prevalent cases	pKARMA	Sweden	5838	25 79	Case-control study	Breast Cancer Association Consortium 2006
II	Rotterdam Breast Cancer Study	RBCS	Netherlands	791	18 84	Hospital based case-control study, Rotterdam area	Easton,D.F. 2007
II	Singapore and Sweden Breast Cancer Study	SASBAC	Sweden	1701	50 74	Population-based case-control study	Wedren,S. 2004
II	Sheffield Breast Cancer Study	SBCS	UK	1266	29 93	Hospital-based case-control study	MacPherson,G. 2004; 679 Rafii,S. 2002
II	Study of Epidemiology and Risk factors in Cancer Heredity	SEARCH	UK	7093	23 69	Population-based case-control study	Lesueur,F. 2005

*Only cases with known European ethnicity were included in the analyses

4.1.1.1 SNP selection (applicable to Studies I and II)

In Study I, following evidence suggesting the involvement of *TP53* network genes in cancer therapy response (Vazquez et al., 2008, 2010, 2011), and suggestive evidence of the prognostic and predictive potential of p53 status, along with NQO1 (Fagerholm et al., 2008), an initial survival study was performed in the HEBCS (n=925) cases for SNPs in the regions of five genes. These five genes — *PRKAG2, PPP2R2B, CCNG1, PIAS1* and *YWHAQ* — were previously identified by Vazquez et al. (2008) by analyzing 187 SNPs residing in 138 TP53 pathway genes for their impact on cancer therapy response *in vitro*. To investigate their effect on breast cancer survival and treatment outcome, the HEBCS sample set was employed to investigate all of the tagging SNPs, available in BCAC/COGS, representing different haplotypes of these genes. Multiple haplotypes in *PRKAG2* and one haplotype in *PPP2R2B* emerged as significant predictors of patient survival in HEBCS. To validate the result, three additional studies, i.e. ABCS, HABCS, PBCS, were added to the study to be investigated individually, and in a pooled data setting. Thus, the analysis in the pooled data (validation) included five SNPs representing different haplotypes in *PRKAG2* and *PPP2R2B*: *PRKAG2*-01 (rs1029946), *PRKAG2*-02 (rs4726050), *PRKAG2*-03 (rs6464153), *PRKAG2*-04 (rs7789699)) and *PPP2R2B* (rs10477313) (Jamshidi et al., 2013).

In Study II, on the basis of published evidence, including the result provided by Fagerholm et al. suggesting the connection between the NF-κB signaling pathway and potential prognostic and predictive markers of breast cancer survival and treatment outcome (Fagerholm et al. 2008), 917 SNPs, which were previously genotyped for BCAC/COGS projects, were selected locating within or in a 50kb flanking region of 75 genes suggested to be the components of the NF-κB pathway activation by KEGG hsa04064 dataset (www.genome.jp/kegg/) (Kanehisa et al., 2014). The selected genes included NF-κB related ligands and receptors (e.g. TNF, TLR1-4, and TNFRSF10A and B), membrane molecules (e.g. IRAK2), kinases (e.g. IKBKB), I-kappa-B cascade (e.g. IKBKG, IRAK1 and TLR8), cytoplasmic sequestering/releasing of NF-κB (e.g. NF-κBIs and TNFSFs), and transcription factors (e.g. NF-κB1 and RELs); but not the T-cell specific elements nor the downstream targets of NF-κB (*Supplementary Table 8* in *Study II*) (Jamshidi et al., 2015).

4.1.2 Tumor array samples

In Studies III and IV, invasive breast carcinoma tumor samples available for TMA (tissue microarray) were used. The NQO1 protein expression and NF-κB nuclear localization (inferred as activation) were studied in two series of invasive breast tumors.

The first series, which was also studied in Study IV for *in situ* detection of miR-30d expression, included 884 tumors from unselected breast cancer patients and an additional 542 familial cases. The unselected cases were ascertained at the Department of Oncology, Helsinki University Hospital, during the years 1997–1998 and 2000 (Syrjakoski et al., 2000; Kilpivaara et al., 2005). The additional 542 familial breast cancer cases were collected by systematic screening for family history at the Department of Oncology, Helsinki University Central Hospital, or were ascertained through genetic counseling at the Department of Clinical Genetics. A total of 1,238 invasive breast carcinomas were available for TMA: 423 from cases without familial background of breast cancer

and 815 from patients with family history. The familial cases were also identifiable as large families with three or more first– or second-degree relatives with breast or ovarian cancer in the family (including the proband), and small families with two affected first-degree relatives (including the proband). Patients with BRCA1 and BRCA2 mutations were identified and excluded from the familial patient series (Vehmanen et al., 1997; Vahteristo et al., 2001, 2002). The tumor samples were collected at surgery prior to adjuvant treatment.

The second series used in Study III included 283 primary tumors of patients with advanced breast cancer who participated in a randomized multicenter trial which compared two drugs, Taxotere (docetaxel) and methotrexate-fluorouracil (MF), after anthracycline failure in metastatic patients (Sjostrom et al., 1999). Of these, 113 primary breast tumors on TMA (Tynninen et al., 2002) were available for our analysis. Of the 113 studied tumors, all were scored for NQO1, while 80 were scored for NF-κB (Jamshidi et al., 2012).

4.1.3 Fresh frozen tumor samples

In Studies I and III, the gene expression microarray analysis was performed on fresh frozen breast cancer tumors. The total RNA from 187 primary breast cancer tumors, including 155 from unselected series and 32 from the additional familial sets, were extracted by the mirVANA miRNA Isolation Kit (Life Technologies, Carlsbad, CA, USA). The samples were further processed, and hybridized into Illumina HumanHT-12 v3 Expression BeadChips containing 24,660 Entrez Gene entities, according to the manufacturer recommendations (http://www.illumina.com). Following the MIAME (Minimum information about a microarray experiment) guideline (Brazma et al., 2001), the collected data was submitted to the GEO (Gene Expression Omnibus) database (GSE24450) (Jamshidi et al., 2012, 2013).

4.2 Clinical and pathological information and tumor characteristics

4.2.1 Studies I and II

Each study participating in BCAC submitted the clinical and pathological data of their subjects including age of diagnosis, tumor grade, size, nodal status, metastases at diagnosis, histological type, estrogen receptor, progesterone receptor, HER2 status, and follow-up and vital status (Broeks et al., 2011). Table 2 lists additional publications by each contributing study in BCAC with detailed description of the data.

4.2.2 Studies III and IV

Clinical and pathological information on tumor characteristics, size, nodal status, distant metastasis, and estrogen and progesterone receptor status was collected from the pathology reports. A breast cancer pathologist re-reviewed all tumors for histological diagnosis and grade according to the Scarff-Bloom-Richardson recommendation, modified by Elston and Ellis (Elston, Ellis, 1991). For

HER2 status collected from the TMA data, the CISH results were prioritized, i.e. CISH result (0–1=neg, 2–3=pos); if CISH results were unavailable IHC was used (less than 10% scored 0–1=neg, and more than 90% scored 3=pos; score 2 was not used) (Jamshidi et al., 2013). For evaluating the p53 expression, breast cancer TMA sections were stained by immunohistochemical methods using mouse monoclonal anti-human p53-antibody (DO-7, DAKO) and 20% cutoff was set to determine positive and negative status (Tommiska et al., 2005). The Ki-67 expression was determined using

Ki-67 antibody (Ahlin et al., 2007) with 20% cutoff set to classify positive and negative status (Jamshidi et al., 2012).

The information on death due to breast cancer or other reason was obtained from the Finnish Cancer Registry. Information on adjuvant treatment and distant metastases during the follow-up was collected from patient records. In Study III, two series of patients were included in the survival analyses: first, the extensive series of sporadic and familial non-BRCA1/2 breast tumors, and second, those in clinical trials comparing chemotherapy regimens after anthracycline treatment failure in metastatic breast cancer.

4.3 Immunohistochemical methods

4.3.1 Protein expression

In Study III, TMA was used to assess NQO1 protein expression and NF-κB nuclear localization. TMA was constructed using a set of four cores (diameter 0.6 mm) per source block, which was the most representative region of each formalin-fixed and paraffin-embedded breast cancer specimen (Tommiska et al., 2005). The mouse monoclonal anti-human NQO1-antibody (Santa Cruz, diluted 1:500) and the rabbit monoclonal anti-human NF-κB (ABCAM, diluted 1:1000) was used to detect NQO1 and NF-κB, respectively. The secondary reagents were from Vector Laboratories (Burlingame, USA), and the chromogenic substrate enhancement step was performed as described, without nuclear counterstaining (Bartkova et al., 2007). For the carriers of homozygous c.558C>T variant, only 0–1% of normal breast tissue or tumor cells were immunohistochemically positive for NQO1, therefore, the cutoff is generally set at 2% to determine the negative and positive status.

Consistent with previous studies (Lessard et al., 2005), and our observation of only rare nuclear positivity in normal or benign breast tissue ($n = 30$), the 5% cutoff was set for NF-κB status classification, i.e. NF-κB was considered positive/activated when 5% or more cancer cells showed nuclear staining and negative when fewer than 5% cells showed nuclear signal. Also, NF-κB was considered negative when only cytoplasmic staining was observed (Jamshidi et al., 2012).

4.3.2 miRNA *in situ* hybridization

In Study IV, miRNA *in situ* hybridization for detecting miRNA expression was done on formalin-fixed paraffin-embedded tissue microarray sections as described previously (Li et al., 2012). The deparaffinization of slides was carried out in a xylene series and the rehydration step was done using an ethanol series (100% to 25%). A ten-minute proteinase K digestion (10ug/ml; Roche) was

followed by slides one hour pre-hybridization in hybridization solution consisting of 50% formamide, 5XSSC, 500 ug/ml yeast tRNA, and 1X Denhardt's solution, as well as overnight hybridization with double digoxigenin labeled miR-30d locked nucleic acid probe (5'-CTTCCAGTCGGGGATGTTTACA-3', 2.5μM; Exiqon) in hybridization solution. The washing step (50% formamide, 2XSSC) was performed at hybridization temperature. The anti-digoxigenin-AP antibody (1:1500 dilution; Roche) and BCIP/NBT substrate (Sigma) were used for the chromogenic identification of signals. The evaluation of the results was performed without knowledge of the clinicopathological information. The staining was classified as no staining, weak, moderate and strong cytoplasmic signals.

4.4 Drug response assay

In Study IV, the association between miR-30 family members and doxorubicin and lapatinib response *in vitro* was examined through a miRNA mimic/inhibitor-based drug response in breast cancer cell lines as described previously (Yadav et al., 2014). The assay ready cell lines used were MCF-7 (ER+, PR+, HER2-, p53 wild-type), MDA-MB-361 (ER+, PR+, HER2+, p53 mutated), HCC1937 (ER-, PR-, HER2-, p53 mutated), and HCC1954 (ER-, PR-, HER2+, p53 mutated). In the validation round, the CAL-120 (ER-, PR-, HER2-, p53 mutated) and MDA-MB-436 (ER-, PR-, HER2-, p53 mutated) cell lines were added to the screening. A custom human miRNA library was obtained from Ambion (mirVana™ miRNA mimic/inhibitor) on 384-well plates and was used with 6 replicates in primary and 11 replicates in the replication/validation round. Table 3 lists the specific miRNA mimics and miRNA inhibitors for each miR-30 family member. MiRNA inhibitors are single-stranded oligonucleotides that bind and inactivate their target miRNA, irreversibly. MiRNA mimics are double-stranded oligonucleotides which mimic the corresponding miRNA. The generic intra-plate controls used in the screens were acquired from QIAGEN and Ambion (pre-miR negative control #2 with 32 replicates, and AllStars Cell Death Control with 12 replicates). The concentrations of doxorubicin were 1, 10, 100, 500, 1,000, and 10,000 nM, and for lapatinib were 0.83, 10, 100, 1,000, 5,000, and 10,000 nM. Cell proliferation was measured 96h after transfection by adding 25 ul per well of CellTiter-Glo (Promega) followed by 5 minutes shaking at 600 rpm (Titramax 1000, Heidolph) and 5 minutes centrifugation at 1000 rpm (SL40R, Thermo Scientific) and luminescence was detected using PHERAstar FS plate reader (BMG Labtech). The secondary screening was done similarly as the primary screen. Fluorescence, indicating the number of dead cells in each well, was measured using the PHERAstar FS plate reader and subsequently, viable cells were detected with CellTiter-Glo 2.0 reagent (Promega) using the Paradigm reader (Beckman Coulter) (Yadav et al., 2014; Pemovska et al., 2013).

Table 3. The specific miRNA mimics and miRNA inhibitors for each miR-30 family member.

miRNA	Product type	Ambion ID	Mature miRNA Sequence
hsa-miR-30a-5p	mirVana miRNA mimc	MC11062	UGUAAACAUCCUCGACUGGAAG
hsa-miR-30a-5p	mirVana miRNA inhibitor	MH11062	UGUAAACAUCCUCGACUGGAAG
hsa-miR-30b-5p	mirVana miRNA mimc	MC10986	UGUAAACAUCCUACACUCAGCU
hsa-miR-30b-5p	mirVana miRNA inhibitor	MH10986	UGUAAACAUCCUACACUCAGCU
hsa-miR-30c-5p	mirVana miRNA mimc	MC11060	UGUAAACAUCCUACACUCUCAGC
hsa-miR-30c-5p	mirVana miRNA inhibitor	MH11060	UGUAAACAUCCUACACUCUCAGC
hsa-miR-30d-5p	mirVana miRNA mimc	MC10756	UGUAAACAUCCCCGACUGGAAG
hsa-miR-30d-5p	mirVana miRNA inhibitor	MH10756	UGUAAACAUCCCCGACUGGAAG
hsa-miR-30e-5p	mirVana miRNA mimc	MC10037	UGUAAACAUCCUUGACUGGAAG
hsa-miR-30e-5p	mirVana miRNA inhibitor	MH10037	UGUAAACAUCCUUGACUGGAAG

4.5 Statistical methods and bioinformatics

4.5.1 Association with tumor characteristics

In Studies I, III and IV, the statistical analyses for association between the candidate markers and tumor characteristics were conducted using IBM SPSS Statistics (SPSS Inc, Chicago, IL, USA). Unless otherwise indicated, *p*-values for evaluation of proportional differences in variants by tumor characteristics were calculated using Pearson's chi-squared tests. Fisher's exact test was used when the number in any category was less than five, and linear-by-linear association chi-squared was used for ordinal and binary variables. The significance limit was set at 0.05 (two-sided test). *P*-values are two-sided.

4.5.2 Survival and treatment analyses

The survival analyses were conducted in IBM SPSS Statistics (SPSS Inc, Chicago, IL, USA) for Studies I, III and IV, and in R environment for statistical biocomputing (www.r-project.org) for Study II. Log-rank tests were used to evaluate the statistical significance of differences between Kaplan–Meier curves. Univariate (non-adjusted) and multivariate (adjusted) Cox regression analyses were used to estimate survival hazard ratios overall and in various subgroups. To test whether the variable is an independent predictor of survival, the multivariate model was adjusted for conventional prognostic markers including grade, tumor size (T), nodal status (N), metastasis at diagnosis (M) (except when the end point was metastasis), ER, PR, HER2, Ki67 status, and p53 status when appropriate. When studies were pooled, all Cox models were also adjusted for study. In the analyses with adjuvant treatment stratifications, sensitivity analyses were conducted by excluding patients who had distant metastasis at the time of diagnosis (M=1) as they had been extensively treated for metastatic disease, and reported if any changes were observed. All *p*-values are from two-sided tests. The drug response package in R, drm, was used to fit logistic curves to the %inhibition curves.

In Study I, in favor of running models including all patients, a category of missing value was included for each separate variable; however, sensitivity analyses were performed which only allowed the inclusion of patients with available information for all variables and the result was reported if any changes were observed. To evaluate the interaction effects between SNPs and tumor feature or treatment, a multivariate Cox regression model was built including the interaction terms as well as the main effects (2df each). The follow up time was measured between the date of diagnosis to the date of death due to breast cancer (for breast cancer survival) or any reason (for overall survival), and right-censored at 10 years. A total of 96% of patients were incident breast cancers (criterion: 6 months from the date of diagnosis) (Jamshidi et al., 2013).

In Study II, the powerSurvEpi package in R was used for power analyses of the survival study. The GWAS-SNPs with a minor allele frequency (MAF) <1%, i.e. rarely presented in the population, were excluded. Two-way SNP interaction analysis was conducted for recessive (AA = 0, Aa = 0, aa = 1) and dominant (AA = 0, Aa = 1, aa = 1) models of inheritance. To evaluate the SNP-SNP interaction effect on patients' survival, the likelihood ratio test was used to compare multivariate Cox regression models of pairs of SNPs with and without an interaction term (SNP1+SNP2 *vs*. SNP1+SNP2+(SNP1*SNP2)) (Jamshidi et al., 2015). Based on the likelihood ratio test, *p*-values of the appropriate models for each SNP pair were selected. The multiple testing error was corrected using the Benjamini-Hochberg post hoc method. The method is also robust against moderate dependency between SNPs, for instance the linkage disequilibrium (Benjamini & Hochberg, 1995; Sarkar, 2002). The significant association criteria for the interaction pairs included two stepwise thresholds. First, the interactive pairs with *p*-value <0.01 after correction were selected. Second, a threshold for the HR based on the power analysis for each model was considered. The 10-year overall survival was defined from the time of diagnosis to the date of death due to breast cancer or other reasons (median follow-up time 5.6 years), or to the date of the last follow-up. To allow for the inclusion of prevalent cases, time at risk was left censored using date of study entry (Jamshidi et al., 2015).

In Study III, for the first set of patients the survival was measured as time between diagnosis to the date of death due to breast cancer or other reasons within 10 years of follow-up, and as 5 years survival from metastasis to death, which means the time from distant metastasis to the date of death. A total of 996 invasive breast tumors were included in the NQO1-related survival analysis with 208 events. A total of 1,030 invasive breast tumors with 220 events were included in the NF-κB-related survival analysis. The median follow-up time for 10-year survival analysis was 112 months. From the second series of patients (n=283), a total of 113 tumors were available for TMA, of which 113 were included in the NQO1-related analysis and 80 in the NF-κB-related analysis. The response was determined based on the WHO recommendations (Miller et al., 1981). Parameters such as treatment response, time to progression (TTP), and overall survival (OS) from start of anthracycline treatment preceding randomization were analyzed. In survival analysis, the clinical response was categorized to response (complete or partial) and non-response (no change and progression). Anthracycline-treated Overall survival (AOS) was calculated as the time between the beginning of anthracycline treatment until death. Anthracycline-treated Time to progression (ATTP) was calculated from the start of anthracycline treatment till disease progression. AOS and ATTP were collectable for 70 and 55 tumors in NQO1 and NF-κB analyses, respectively. Time to progression

(TTP) on methotrexate-5-FU or docetaxel was calculated as time between the date of randomization and disease progression (Jamshidi et al., 2012).

In Study IV, the survival time was calculated for 10 years breast cancer survival (BCS), i.e. the time from diagnosis to the date of death due to breast cancer, and 5 years breast cancer death or distant metastasis (BDDM), i.e. time between diagnosis and distant metastasis or breast cancer death, or the end of follow-up time within five years. All patients included in this study were incident cases: entering the study before or in less than 6 months from the date of diagnosis.

4.5.3 Expression quantitative trait loci (eQTL) analysis

In Study II, data from The Cancer Genome Atlas (TCGA) and METABRIC project (Curtis et al., 2012; Dvinge et al., 2013) was applied to evaluate the correlation between the candidate loci and gene expression by cis-eQTL analysis which was conducted with R package Matrix eQTL (Shabalin, 2012) using linear regression and ANOVA models. Peripheral blood DNA SNP genotyping data, as well as expression data, were obtained for 913 primary breast tumors available in TCGA dataset. Additionally, expression data of healthy breast tissues was retrieved for 85 out of the 913 TCGA cases. The TCGA expression data is from level 4 RNA-Seq (upper quartile normalized RSEM expression estimates). TCGA-matched peripheral blood DNA SNP genotype data is from level 2 Birdseed files (genotyped on Affymetrix Genome-Wide Human SNP Array 6.0 and processed using Birdseed). The METABRIC data (genotyped on Affymetrix SNP 6.0 platform) was retrieved from the European Genome-phenome Archive (cancergenome.nih.gov). The raw genotype data was processed by the Affymetrix Genotyping Console Software, according to the instruction of Affymetrix Best Practices SNP 6.0 Analysis Workflow. The quality control was done by Contrast QC, with the sample quality threshold of <0.4 and genotype calling by Birdseed v2 with call rate threshold set at >95%. The process resulted in altogether 1,328 samples with both genotype and expression data from breast tumor tissues (Jamshidi et al., 2015).

4.5.4 Gene expression microarray analysis

In Studies I and III, the raw data was imported into R (http://cran.r-project.org) and analyzed by methods included in Bioconductor facilities (Gentleman et al., 2004), and quality checked according to the Illumina microarray pipeline (Du, Kibbe & Lin, 2008). The data was normalized by the quantile method (Bolstad et al., 2003). The gene expression matrix was formed by averaging the probes which were matched to the same Entrez Gene IDs (Tatusova, 2010). The Pearson's correlation was evaluated for each gene expression and the nominal *p*-values were adjusted with Benjamini–Hochberg post hoc correction. The threshold for corrected *p*-value for further analyses and functional annotation was set for less than 0.01 (Benjamini & Hochberg, 1995). In Study IV, the gene expression analysis in METABRIC was conducted in R using Spearman's rank correlation. Functional annotation and enrichment analyses were studied using the DAVID microarray functional annotation tool and Ingenuity Pathway Analysis (IPA) (QIAGEN Inc., https://www.qiagenbioinformatics.com/products/ingenuity-pathway-analysis) (Jamshidi et al., 2012, 2013).

4.6 Ethical aspects

All studies were carried out with patients' written informed consent and the permission from the Helsinki University Hospital Ethical Committee (Dnro207/E9/07 and Dnro272/13/03/03/2012). Each study contributing to BCAC shared data according to the ethical framework and followed national protocol for patients' participation and was approved by the appropriate local institutional review committee. All studies were performed following the reporting recommendations for tumor marker prognostic study (REMARK) (McShane et al., 2006).

5 Results

5.1 Germline variations in TP53 network genes

Study I investigated the association between the germline variations in five TP53 network genes which were previously suggested to impact drug response *in vitro* (Vazquez et al., 2008, 2010, 2011), i.e. *PRKAG2, PPP2R2B, CCNG1, PIAS1* and *YWHAQ,* and breast cancer patients' survival and treatment outcome. The studied variations included all the SNPs in regions of these five genes which were available from a previously genotyped GWAS case-control study (Li et al., 2010, 2011). The initial study population was HEBCS (n=925). Five SNPs — namely, *PRKAG2*-01 (rs1029946), *PRKAG2*-02 (rs4726050), *PRKAG2*-03 (rs6464153), *PRKAG2*-04 (rs7789699), *PPP2R2B* (rs10477313) — which showed significant survival association in HEBCS (*Supplementary Table 1* in *Study I*) were further analyzed in the pooled data including the additional BCAC studies, i.e. ABCS (n=1,442), HABCS (n=794), and PBCS (n=1,540) (*Tables 1* and *2* in *Study I*). Additionally, we investigated the survival and therapy impact of the interaction of these SNPs with *TP53* R72P and *MDM2* SNP309 which were previously suggested to have a combined effect on patients' survival (Schmidt et al., 2009). With the exception of *TP53* R72P, all of the SNPs exhibited some variation in genotype frequency among the studies (*Supplementary Table 2* in *Study I*), due to different allele frequencies in different populations.

5.1.1 Association with tumor clinical and pathological features

Tumors homozygous for *PRKAG2*-01 (rs1029946) rare G allele were more often TP53-negative ($p = 0.005$). Homozygous carriers of *PRKAG2*-02 (rs4726050) rare G allele less often developed high grade tumors ($p = 0.005$) whereas *PRKAG2*-04 (rs7789699) rare A allele carriers were frequently of high grade tumors ($p = 0.001$), with a dose-dependent effect of the rare allele associating with higher grade (Chi square for trend: $p = 0.002$). Also, the progesterone receptor negative status was more frequent in homozygous carriers of *PPP2R2B* (rs10477313) rare A allele ($p = 0.002$) (*Supplementary Table 3* in *Study I*).

5.1.2 Association with patients' survival

The association between SNPs in *PRKAG2* and *PPP2R2B* was analyzed in pooled data using the univariate (non-adjusted) and multivariate (adjusted) Cox regression models. The multivariate model was adjusted for conventional prognostic markers, i.e. grade, T, N, M, ER, PR, as well as study and age of diagnosis. *Supplementary Table 3* in *Study I* illustrates the hazard estimates of both univariate and multivariate analyses for SNPs with significant survival association. Patients carrying homozygous *PRKAG2*-01 (rs1029946) rare G allele had improved 10-year overall survival compared to carriers of the common A allele ($HR_{non\text{-}adjusted} = 0.53$, 95% CI = 0.3–0.9; $p = 0.023$ for GG vs. AA/AG). The effect is visualized with Kaplan–Meier plots (*Figure 1a* in *Study I*). The result was also consistent among all the studies in the pooled data (*Supplementary Table 5* in *Study I*). *PRKAG2*-01 (rs1029946) remained an independent predictor of survival after adjustment for

conventional prognostic markers as well as age of diagnosis and study ($HR_{adjusted}$ = 0.57, 95% CI = 0.3–0.9; p = 0.044). An additional multivariate Cox regression model was built by adding the p53 status to the model because of the observed association between *PRKAG2*-01 (rs1029946) and p53 tumor status. Although the number of patients with complete information for all variables which could be included in this model was highly reduced, the overall survival remained the same but it was no longer significant ($HR_{adjusted}$ = 0.54, 95% CI = 0.2–1.0; p = 0.137 for GG vs. AA/AG).

We observed suggestive evidence of lower risk of death for carriers of *PRKAG2*-02 (rs4726050) rare G allele (AG/GG) compared to AA carriers ($HR_{non\text{-}adjusted}$ = 0.85, 95% CI = 0.7–0.9; p = 0.049 for AG/GG vs. AA) (*Figure 1b* in *Study I*). The hazard estimate was not consistent among the studies, i.e. HABCS (HR = 1.18, 95% CI = 0.8–1.7) (*Supplementary Table 6* in *Study I*), and the association was not significant in the multivariate model. For the rest of the SNPs, we observed nominally significant association with patients' survival (*Supplementary Table 3* in *Study I*); however, the effect seems to be driven only by the discovery HEBCS population with no effect on the other studies. The survival association observed in HEBCS for the remainder of SNPs, namely, *PRKAG2*-03 (rs6464153) and *PRKAG2*-04 (rs7789699), was not found in the pooled data. Also, none of the studied SNPs showed significant association with patients' survival in the respective subgroups of p53-positive and ER-positive observed in the discovery analyses.

To investigate the combined effect of each of the studied SNPs with either *TP53* R72P or *MDM2* SNP309, the survival analyses were stratified by these two SNPs. Patients carrying the *PRKAG2*-02 (rs4726050) rare G allele had better breast cancer survival confined only to *MDM2* SNP309 rare G allele carriers ($HR_{non\text{-}adjusted}$ = 0.45, 95% CI = 0.2–0.7, p = 0.001 for *PRKAG2*-02 GG in MDM2 SNP309 TG/GG compared to the rest of the carriers). *Figure 2* in *Study I* illustrates the Kaplan–Meier plots of cumulative survival for patients carrying each *PRKAG2* (rs4726050) genotype within one group of *MDM2* SNP309 genotype. Moreover, in a multivariate Cox regression model, including the interaction term as well as the main effects (2df each), the interaction association with survival remained significant ($HR_{adjusted}$ = 0.59, 95% CI = 0.3–0.9; p = 0.047). There was no indication of significant interaction between the remaining SNPs and either of *TP53* R72P or *MDM2* SNP309.

Patients carrying *PP2R2B (rs*10477313) rare A allele (GA/AA) had increased survival compared to the carriers of GG genotype (p = 0.018) (*Figure 3a* and *Table 3* in *Study I*). The effect also remained significant when corrected for conventional prognostic factors using the multivariate Cox regression model ($HR_{adjusted}$ = 0.83, 95% CI = 0.7–0.9; p = 0.034) (*Table 3* in *Study I*). To evaluate the impact of the studied SNPs and treatment outcome, the dataset was stratified by either chemotherapy or hormonal treatment. Of the studied SNPs, *PPP2R2B* (rs10477313) appeared to associate with patients' survival after adjuvant hormonal therapy, i.e. patients carrying rare A allele (GA/AA) had improved overall survival compared to GG genotype carriers ($HR_{non\text{-}adjusted}$ = 0.66, 95% CI = 0.5–0.9; p = 0.048 for GA/AA vs. GG), whereas no differential survival was observed among those who had not received hormonal treatment ($HR_{non\text{-}adjusted}$ = 0.87, 95% CI = 0.7–1.1; p = 0.200) (*Figure 3* and *Table 3* in *Study I*).

5.1.3 Association with gene expression level, and functional annotation

There was no significant correlation between the SNPs in *PRKAG2* and *PPP2R2B* SNPs and gene expression in the HEBCS dataset. However, the gene expression analysis of microarray data of 187 Finnish cases with primary breast tumors (*Supplementary Table 2* in *Study I*) showed that higher *PRKAG2* expression associates with decreased breast cancer patient survival (HR = 8.6, 95% CI = 1.3–56.1, p = 0.024) (*Supplementary Figure 1* in *Study I*). Additionally, the higher expression level of *PPP2R2B* correlated with improved patient survival (HR = 0.03, 95% CI = 0.002–0.565, p = 0.019) (*Supplementary Figure 2* in *Study I*). The limited number of patients in a hormone-treated subset of patients did not allow for the survival analysis by *PPP2R2B*.

5.2 Germline variations in NF-κB network genes

In Study II, to evaluate the association between germline variations in the NF-κB activating pathway and patients' survival, a set of markers including 917 SNPs residing within or in the 50kb flanking region of 75 candidate genes involved in the activation of the NF-κB pathway was applied. The panel of markers used in this study was provided by a custom Illumina iSelect genotyping array (iCOGS) designed for the Collaborative Oncological Gene-environment Study (COGS) (Michailidou et al., 2013). A total of 24 BCAC studies contributed to this study with altogether 30,431 invasive breast cancer cases of European ancestry (Table 2). Using a multivariate Cox regression model (see section 4.5.2), this study focused on two SNP interactions and their association with patients' survival and treatment outcome under both recessive (AA = 0, Aa = 0, aa = 1) and dominant (AA = 0, Aa = 1, aa = 1) models. Given the sample size (n = 30,431, death = 3,375) and the average MAF of 23.4%, the analysis carried 80% power to identify survival association with HR above 1.4 (or 1/1.4 = 0.6) and HR of 6.2 (or 1/6.2 = 0.16) in the dominant and recessive models respectively.

5.2.1 Association with patients' survival

Under the recessive model, a pairwise interaction between rs5996080 (A/G, MAF = 8%) and rs7973914 (G/A, MAF = 40%) was observed to associate with patients' survival, i.e. carriers of the homozygous rare allele for both SNPs (rs5996080-GG, rs7973914-AA) showed poor overall survival compared to carriers of at least one common allele ($HR_{interaction}$ = 6.98, 95% CI = 3.3–14.4, p = 1.42E-07) (*Table 1* in *Study II*). Also, the likelihood ratio test comparing multivariate Cox regression models assuming no interaction versus the model with the interaction term indicated that the interaction term was an improved predictor of survival ($p_{likelihood\text{-}ratio\text{-}corrected}$ = 0.003) (*Table 1* in *Study II*). The comparison of absolute uncorrected survival rates of genotype combination is illustrated by Kaplan–Meier plots (*Figure 1* in *Study II*). The same interaction analyses were conducted for SNPs in linkage disequilibrium with the interacting pair (*Supplementary Table 3* in *Study I*). Due to the limited number of events (<5), no subgroup analyses were conducted for the interacting SNP pair.

The SNP rs5996080 of the recessive pair is located on chromosome 22 at 31.5kb downstream of NF-κB pathway gene *BAFFR* (B-cell activating factor receptor, also known as *TNFRSF13C*). There is strong linkage disequilibrium (r^2 = 1) with 15 SNPs residing in *BAFFR*. rs7973914 resides in chromosome 12, and lies 8kb upstream of the NF-κB pathway gene *TNFR3* (TNFR superfamily member 3, also known as *LTBR*) and 27kb upstream of *TNFR1* (TNFR superfamily member 1a, also known as *TNFRSF1A*). The haplotype surrounding rs7973914 is short with very few SNPs on it.

Under the dominant model, an interacting SNP pair (rs17243893 (A/G, MAF = 5%) and rs57890595 (A/C, MAF = 11%)) was found to associate with patient survival, i.e. patients carrying at least one rare allele for both variants (rs17243893-AG+GG, rs57890595-AC+CC) had improved overall survival compared to those with common homozygous genotypes ($HR_{interaction}$ = 0.51, 95% CI = 0.3–0.6, p = 2.19E-05) (*Table 2* in *Study II*). When comparing the two multivariate models with and without the interaction term, the interaction was statistically significant ($p_{likelihood\text{-}ratio\text{-}corrected}$ = 0.005) (*Table 2* in *Study II*), *Figure 2* in *Study II* illustrates the Kaplan–Meier curves of the differential survival among genotype combination categories. Similar interaction analyses performed for SNPs in linkage disequilibrium with the interacting pair are listed in *Supplementary Table 4* in *Study II*. The survival association of the interacting SNP pair was consistent among the subgroups but there was no differential association confined to any specific subgroup.

The SNP rs17243893 resides on chromosome 9, and lies in the intron of NF-κB pathway gene *TRAF2* (TNF receptor associated factor 2). The other SNP, rs57890595, is on chromosome 8, within the intron of NF-κB pathway gene *TRAIL-R4* (TNF-related apoptosis ligand receptor 4, also known as *TNFRSF10D*). Two other NF-κB pathway genes nearby this SNP include *TNFRSF10A* and *TNFRSF10C*.

5.2.2 Association with tumor clinical and pathological features

Of the two interacting SNP pairs, the genotype combinations of the pair found under the dominant model (rs17243893 and rs57890595: Aa+aa+Bb+bb *vs* the rest) associated with nodal status (N) (p = 0.010), and might associate with metastasis at diagnosis (M), although it is not statistically significant (*Supplementary Tables 6a* and *b* in *Study II*).

5.2.3 Association with gene expression level, and functional annotation

Using TCGA and METABRIC datasets, the eQTL analysis was conducted to investigate the association between the interacting SNP pairs and the expression level of the corresponding genes in the NF-κB activating pathway. All genotyped SNPs in linkage disequilibrium with the interacting SNP pairs (r^2 > 0.1) were analyzed. The SNP pairs were available in neither TCGA nor METABRIC but they were represented through linkage disequilibrium.

For the interacting SNP pair under the recessive model, the rs5996080 proxy (rs9620000, $r^2 = 1$) correlated with elevated level of *BAFFR* in both the TCGA tumor ($p = 0.049$) and METABRIC datasets ($p = 0.003$). Moreover, other rs5996080 proxies also associated with the expression level of *TNFR1* and *TNFR3,* which are the corresponding genes to the other SNP in this interacting SNP pair. In detail, the rs5996080 proxy (rs17002737, $r^2 = 0.79$) correlated with the expression level of *TNFR1* ($p = 0.049$), with multiple other SNPs in the locus positively associating with the expression of *TNFR3* (rs2269658: $r^2 = 0.5$, D' = 0.8, $p = 0.00006$; rs9620000: $r^2 = 1$, $p = 0.003$; rs5996088: $r^2 = 1$, $p = 0.002$; rs1023497: $r^2 = 0.4$, D' = 1, $p = 0.01$; and rs133367 $r^2 = 0.2$, D' = 1, $p = 0.04$). The number of rs7973914 proxies available in both datasets was limited to four, and none of them showed significant association with the expression level of *TNFR1/3* or *BAFFR*.

The few proxies available for rs17243893 in the interacting SNP pair under the dominant model (rs17243893 and rs57890595) did not show any significant association with the expression level of *TRAF2*, nor with *TRAIL-R4*. An rs57890595 proxy in the TCGA tumor data (rs12546238, $r^2 = 0.2$), and one (rs4278155, $r^2 = 0.2$) in the normal tissue data ($n = 85$), associated with the level of *TRAIL-R4* ($p = 0.004$). Additionally, in the METABRIC dataset, an rs57890595 proxy (rs4871880, $r^2 = 0.1$) correlated with the expression of *TRAF2* ($p = 0.0006$).

The ENCODE-based functional annotations at the Haploreg and RegulomeDB databases of human mammary epithelial cells (HMEC) were used to study the functional role of the interacting SNP pairs or their proxies, and to investigate the possibility of the SNPs locating in the genomic regulatory elements. A total of 35 proxies for rs5996080, from the recessive SNP pair, were likely to modify the transcription factor binding motifs, histone modifications, DNase sites and protein binding regions in HMEC. Out of the 35 SNPs, 26 were in strong LD with rs5996080 (r^2 and/or D' > 0.8). The regulatory annotation identified 22 SNPs in regions with enhancer histone marks, 10 SNPs in promoter histone marks, and 6 SNPs in Dnase hypersensitivity sites (*Supplementary Table 7a* in *Study II*). In addition to *SREBF2* (the host gene for rs5996080), ENCODE annotated genes corresponding to the above-mentioned regulatory modifications included *BAFF*, *MEI1,* and *SHISA8*. An rs5996080 proxy (rs117492772, $r^2 = 0.86$) was annotated to modify the putative transcription factor binding motif of NF-κB. Also, rs5996080 is predicted to alter the putative motif binding of Erα-a. For the other SNP in the interacting pair, rs7973914, four proxies were identified to reside in the regulatory regions with enhancer histone marks in HMEC (*Supplementary Table 7b* in *Study II*). The SNP pair in the dominant model, 17243893 and rs57890595, were located in short haplotype/undefined haplotypes and therefore, the *in silico* analyses were limited. Two rs17243893 proxies (rs17243893 and rs35253986, $r^2 = 1$ and 0.27, respectively) were identified which were mapped to regions with enhancer histone mark and Dnase hypersensitivity sites in HMEC dataset (*Supplementary Table 7c* in *Study II*).

5.3 NQO1 protein expression and NF-κB activation

To investigate the clinical implication of NQO1 and NF-κB expression, an immunohistochemical study was conducted in two series of breast cancer patients' tumors, i.e. the primary tumors of a series of unselected patients and additional familial cases, and the primary tumors of a series of

patients who had been treated for metastatic disease. Of the 1,238 tumors available for TMA in the first series of patients, NQO1 and NF-κB staining results were retrieved for 996 (80%) and 1,030 (83%) tumors, respectively (*Figure 1* in *Study III*). NQO1-positive expression was observed in 823 (83%) and NF-κB nuclear localization (inferred activation) was found in 117 (11%) of the tumors. Since there was no difference in NQO1 expression and NF-κB activation by familial history (*Tables 1* and *2* in *Study III*) all tumors were combined for the analyses. In the second set of patients, the NQO1 and NF-κB staining results were available for 113 and 80 tumors, respectively. Positive expression of NQO1 was found in 64% and NF-κB activation was found in 15% of the analyzable tumors, respectively (*Supplementary Table I* in *Study III)*.

5.3.1 Association with tumor clinical and pathological features

The expression of NQO1 and the nuclear localization/activation of NF-κB inversely correlated with each other ($p = 0.012$). Moreover, a direct association was found between NQO1-negative expression and the ER-negative status of the tumors ($p = 0.011$). In line with the published impact of the NQO1*2 (rs1800566) variation, the expression of NQO1 correlated with NQO1*2 (rs1800566) homozygous rare T allele ($p < 0.0001$). Tumors with TT (Ser/Ser) genotype were all NQO1 protein negative (n=24, 100%), whereas tumors with homozygous wild-type C allele (Pro/Pro) (n=171/264, 64%) as well as heterozygous genotype carriers (n=541/573, 94%) were NQO1-positive (*Table 1* in *Study III*). Nuclear localization/activation of NF-κB associated with tumors of ductal carcinomas ($p = 0.017$), ER-positive status ($p = 0.001$), and those of the lower grade ($p = 0.014$) (*Table 2* in *Study III*). There was no significant association between either NQO1 expression or NF-κB activation and the clinicopathological feature of tumors in the second series of patients (*Supplementary Tables 2* and *3* in *Study III*).

5.3.2 Association with patients' survival

NQO1 protein expression did not modify the survival pattern among all patients or in subgroups of patients who had received chemotherapy (*Figure 2* and *Table 3* in *Study III*). Similarly, in the second series of patients who have received chemotherapy for the metastatic disease, there was no significant association between NQO1 protein expression and patients' overall survival, or in subgroup analyses stratified for first-line anthracycline treatment or after second-line docetaxel treatment (*Supplementary Figures 1a–c* and *Table 4* in *Study III*). Negative expression of NQO1 appeared to accelerate the progression of the disease after second-line methotrexate-fluorouracil therapy (HR = 1.99, 95% CI = 1.04–3.78, $p = 0.03$) (*Supplementary Figure 1d* and *Table 4* in *Study III*). No significant association was found between the nuclear localization/activation of NF-κB and patients' survival in either of the datasets (*Figure 3* and *Supplementary Figure 2* in *Study III*). In both series of patients, the NQO1 and NF-κB expression appeared to have an inverse pattern of survival after adjuvant anthracycline treatment (poor survival for patients with negative NQO1 or nuclear localization/activation of NF-κB); however, the trend was not statistically significant (*Figures 2* and *3* and *Tables 3* and *4* in *Study III*).

5.3.3 Association with gene expression level, and functional annotation

The microarray analysis of total RNA extracted from 183 primary breast tumors revealed 877 genes, which significantly correlated with *NQO1* expression (293 positively and 584 negatively correlated) and 2,871 genes significantly correlated to *NF-κB1* expression (1,635 positively and 1,236 negatively) with adjusted *p*-value < 0.01 *(Supplementary Tables 4* and *5* in *Study III)*. Of the genes negatively correlating with *NQO1* are *TNF*, along with 12 other genes linked to the *TNF/NF-κB* pathway, and four genes connected to the toll-like receptor (TLR) family. Of the total of 193 genes correlated with both *NQO1* and *NF-κB1,* only one gene, *LIMA1,* positively correlated with both of them, whereas 59 genes correlated positively with *NQO1* but negatively with *NF-κB1*, and 133 genes correlated positively with *NF-κB1* but negatively with *NQO1* (*Supplementary Table 6* in *Study III*). None of the genes showed negative correlation with both *NQO1* and *NF-κB1*.

The observed opposite pattern was also reflected in the functional annotation of the gene families correlated with *NQO1* and *NF-κB1*. The genes with functions known to be related to *NQO1*, i.e. oxidation/reduction, lipid biosynthesis, steroid metabolism, and endoplasmic reticulum positively correlated with *NQO1* and negatively correlated with *NF-κB1*. Consistently, gene families connected to immune response, lymphocyte activation, JAK-STAT signaling, and apoptosis, which are known to associate with NF-κB pathways, were significantly overabundant among the group which positively correlated with *NF-κB1* and negatively correlated with *NQO1* (*Figure 4* in *Study III*).

5.4 miR-30 family members

In a series of sporadic and familial cases, the *in situ* hybridization (ISH) was performed to assess the expression of miR-30d in 1,238 invasive breast carcinomas available for TMA studies. The miR-30d expression level was studied for its association with patients' survival, as well as the clinicopathological characteristics of the tumor. Furthermore, drug sensitivity screening was conducted to evaluate the impact of the entire miR-30 family members on drug response in breast cancer cell lines *in vitro*. Of 1,238 tumor samples, miR-30d *in situ* hybridization results were obtained for 1,193 (96.3%) tumors: 361 (30.3%) tumors had none or low and 832 (69.7%) tumors had high intensity of cytoplasmic staining (*Figure 1* in *Study IV*). The miR-30d expression levels were not assessed for the remaining 45 (3.7%) tumors, due to loss of cores during the sectioning or staining steps, or cores not containing enough tumor material. However, since no difference was observed in gene expression, clinical and pathological association and survival rates neither between miR-30d absent and low tumor expression nor between intermediate and high expression, the groups were combined for analysis, i.e., "low expression" = absent and low tumor expression and "high expression" = intermediate and high expression.

5.4.1 Association with tumor clinical and pathological features

Increasing miR-30d expression associated with ductal histopathological type (p = 0.003), higher tumor grade (p = 0.0002), positive nodal status (p = 0.007) and higher proliferation rate estimated by Ki67 (p = 0.014). Moreover, tumors with higher miR-30d expression were more frequently ER/PR+HER2+ whereas those with lower miR-30d expression were more often ER/PR+HER2- (p = 0.032) (Table 4).

Table 4. Association of miR-30 expression level with tumor features (unpublished data).

	miR-30d			
	Total	*Low*	*High*	*p.*
	n(%)			
Tumour histology				
Ductal carcinomas	838	233	605	**0,003**
	70,2%	64,5%	72,7%	
Lobular carcinomas	222	90	132	
	18,6%	24,9%	15,9%	
Medullary carcinomas	15	3	12	
	1,3%	0,8%	1,4%	
Other	118	35	83	
	9,9%	9,7%	10,0%	
Grade				
1	281	96	185	**0.0002**
	23,9%	27,0%	22,5%	
2	547	183	364	
	46,5%	51,5%	44,3%	
3	349	76	273	
	29,7%	21,4%	33,2%	
Tumor size				
1	694	213	481	0,417
	58,9%	60,2%	58,3%	
2	410	115	295	
	34,8%	32,5%	35,8%	
3	40	16	24	
	3,4%	4,5%	2,9%	
4	35	10	25	
	3,0%	2,8%	3,0%	

Nodal status				
Negative	645	214	431	**0,007**
	54,9%	61,0%	52,4%	
positive	529	137	392	
	45,1%	39,0%	47,6%	
Metastasis at diagnosis				
Negative	1 147	347	800	1,000
	97,0%	96,9%	97,0%	
Positive	36	11	25	
	3,0%	3,1%	3,0%	
ER status				
Negative	234	70	164	0,872
	20,6%	21,0%	20,5%	
Positive	900	263	637	
	79,4%	79,0%	79,5%	
PR status				
Negative	379	124	255	0,113
	33,5%	37,0%	32,0%	
Positive	753	211	542	
	66,5%	63,0%	68,0%	
p53 tumor status				
Negative	899	264	635	0,160
	80,1%	82,8%	79,0%	
Positive	224	55	169	
	19,9%	17,2%	21,0%	
HER2 status				
Negative	984	298	686	0,064
	87,1%	90,0%	85,9%	
Positive	146	33	113	
	12,9%	10,0%	14,1%	
Ki67 tumor status (proliferation marker)				
Negative	786	250	536	**0,014**
	67,2%	72,5%	65,0%	
Positive	383	95	288	
	32,8%	27,5%	35,0%	
TOP2A tumor status (proliferation marker)				
Negative	573	180	393	**0,001**
	60,6%	69,5%	57,2%	
Positive	373	79	294	
	39,4%	30,5%	42,8%	
SubTypes				
ER/PR pos and HER2 neg	778	232	546	**0,032**
	72,6%	76,1%	71,2%	
ER/PR pos and HER2 pos	91	14	77	
	8,5%	4,6%	10,0%	
ER/PR neg and HER2 pos	52	17	35	
	4,9%	5,6%	4,6%	
ER neg and PR neg and HER2 Neg	151	42	109	
	14,1%	13,8%	14,2%	

Low=None or weak cytoplasmic staining, High=moderate or high cytoplasmic staining

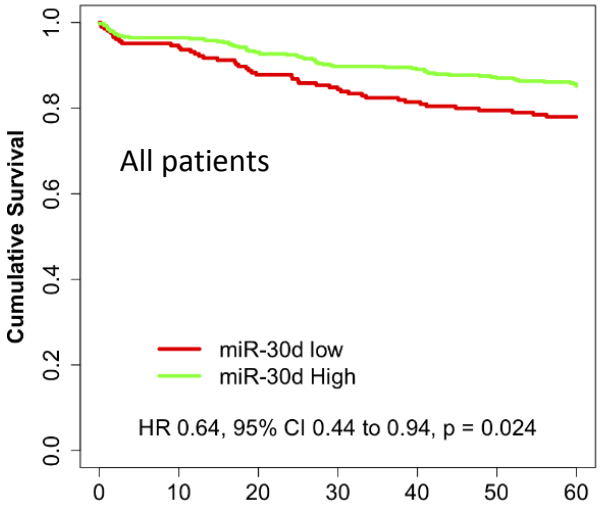
5.4.2 Association with patients' survival

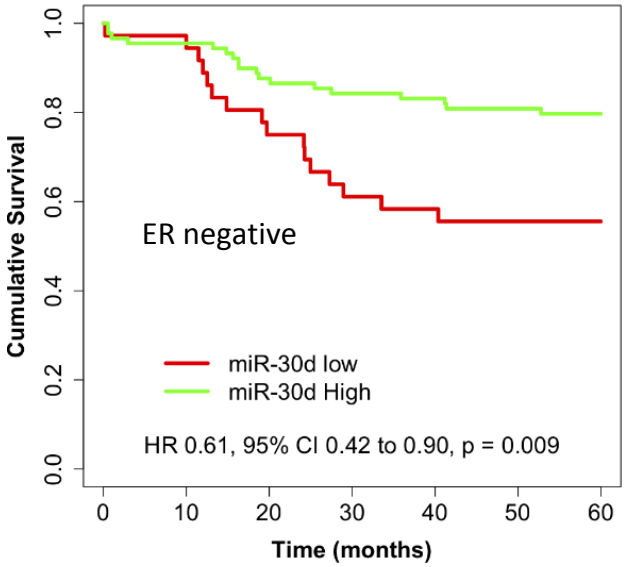
In order to avoid long-term survivors in ascertainment, the survival analyses were performed only among the incident cases. Among the 659 incident cases, 205 (31.1%) had none or low and 454 (68.9%) had high level of miR-30d expression. The endpoint used in the survival analyses was five years breast cancer death or distant metastasis free survival (5-year BDDM). Increased miR-30d expression associated with improved patients' survival (HR = 0.64, 95% CI = 0.44–0.94, p = 0.024). The expression of miR-30d remained an independent predictive factor of 5-year BDDM in a multivariate Cox regression model adjusted for common prognostic factors (HR = 0.44, 95% CI = 0.29–0.66, $p < 10^{-3}$). In the subgroup analysis, the increased level of miR-30d associated with improved 5-year BDDM among patients with: ER-negative tumors compared to ER-positive (p = 0.009); HER2-positive tumors compared to HER2-negative (p = 0.004); highly proliferating tumors indicated by high expression of Ki67 (p = 0.0002); patients with p53-positive (mutated) tumors compared to p53-negative (p = 0.011); and among patients who received anthracycline-based chemotherapy compared to those who did not (p = 0.028) (Table 5). The absolute uncorrected survival difference is illustrated by Kaplan–Meier curves in Figure 5.

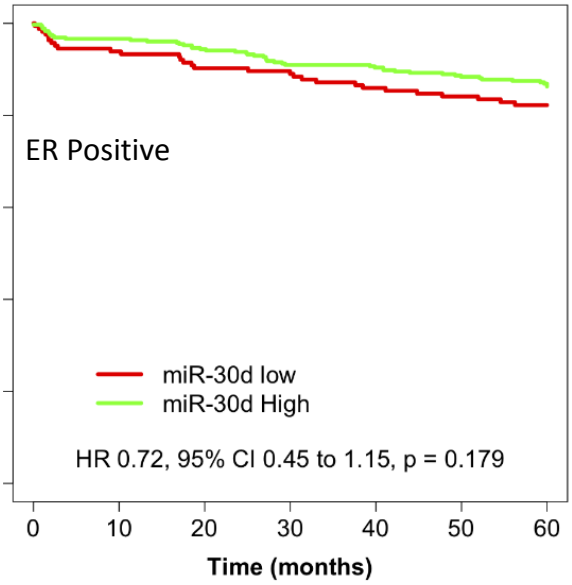
Table 5. For 5-year breast cancer death or distant metastasis of incident cases: A) Univariate Cox regression analysis by miR-30d in all patients, and by miR-30d in patients subgrouped by ER, HER2, Ki67, and chemotherapy status. B) The multivariate Cox regression analysis by miR-30d was adjusted for conventional prognostic factors, i.e. grade, tumor size, nodal status, ER (from medical records; cut-off: >10% as positive, ≤10% as negative), PR (same as ER), Ki67 (cut-off: ≥20% as high, <20% as low), and HER2 (CISH cut-off: ≥90% as positive, <10% as negative) (unpublished data).

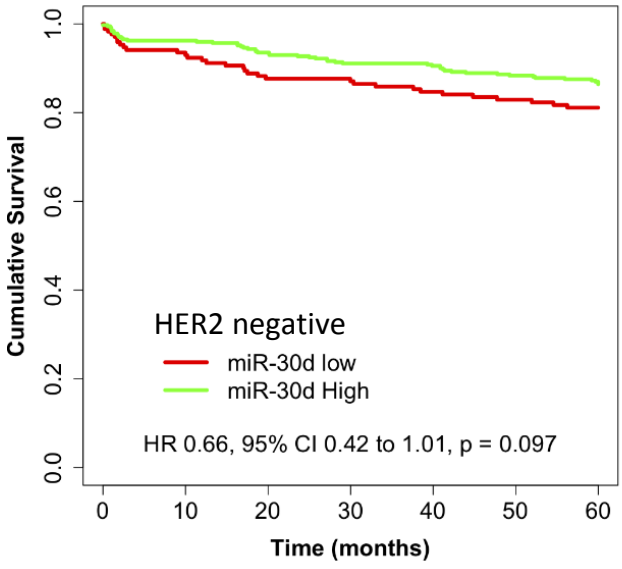
	5-year BDDM				
Category	**miR-30d n(death)**		**p value**	**HR**	**95% CI**
	Low	**High**			
A)					
Univariate Cox's regression analysis by miR-30d in					
All patients	205 (45)	451 (66)	**0,024**	0,64	0,44-0,94
Patients with ER-negative tumors	36 (16)	89 (18)	**0,009**	0,61	0,42-0,91
Patients with ER-positive tumors	164 (29)	356 (48)	0,179	0,72	0,45-1,15
Patients with HER2-negative tumors	170 (32)	371 (50)	0,097	0,66	0,42-1,01
Patients with HER2-positive tumors	18 (12)	61 (15)	**0,004**	0,34	0,16-0,71
Patients with Ki67-negative tumors	135 (19)	261 (32)	0,673	0,88	0,51-1,55
Patients with Ki67-positive tumors	64 (26)	188 (34)	**0,0002**	0,38	0,23-0,64
Patients with TP53-negative tumors	155 (29)	340 (44)	0,16	0,67	0,42-1,07
Patients with TP53-positive tumors	29 (13)	97 (21)	**0,011**	0,41	0,20-0,81
No Anthracycline treatment	74 (23)	196 (34)	0,285	0,74	0,43-1,28
Anthracycline treatment	131 (22)	254 (32)	**0,028**	0,51	0,31-0,87
B)					
miR-30d High vs. low			**0,00007***	0,44	0.29-0.66

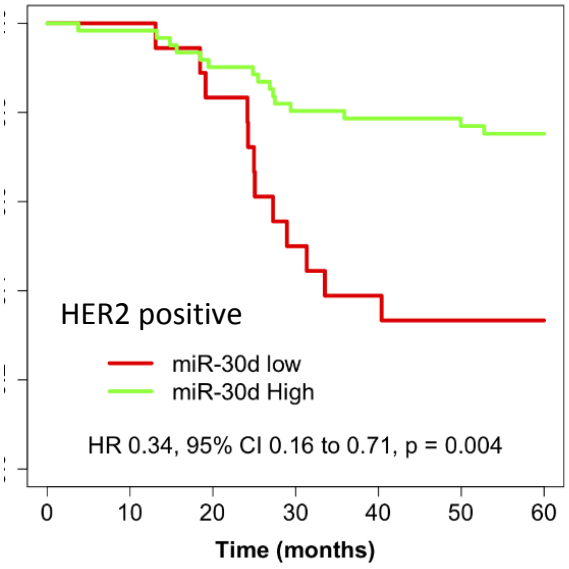
***adjusted for grade, T, N, ER, PR, HER2


Cumulative Survival
0.0
0.2
0.4
0.6
0.8
1.0
All patients
miR-30d low
miR-30d High
HR 0.64, 95% CI 0.44 to 0.94, p = 0.024
0
10
20
30
40
50
60


Cumulative Survival
0.0
0.2
0.4
0.6
0.8
1.0
ER negative
miR-30d low
miR-30d High
HR 0.61, 95% CI 0.42 to 0.90, p = 0.009
0
10
20
30
40
50
60
Time (months)


ER Positive
miR-30d low
miR-30d High
HR 0.72, 95% CI 0.45 to 1.15, p = 0.179
0
10
20
30
40
50
60
Time (months)


Cumulative Survival
0.0
0.2
0.4
0.6
0.8
1.0
HER2 negative
miR-30d low
miR-30d High
HR 0.66, 95% CI 0.42 to 1.01, p = 0.097
0
10
20
30
40
50
60
Time (months)


HER2 positive
miR-30d low
miR-30d High
HR 0.34, 95% CI 0.16 to 0.71, p = 0.004
0
10
20
30
40
50
60
Time (months)

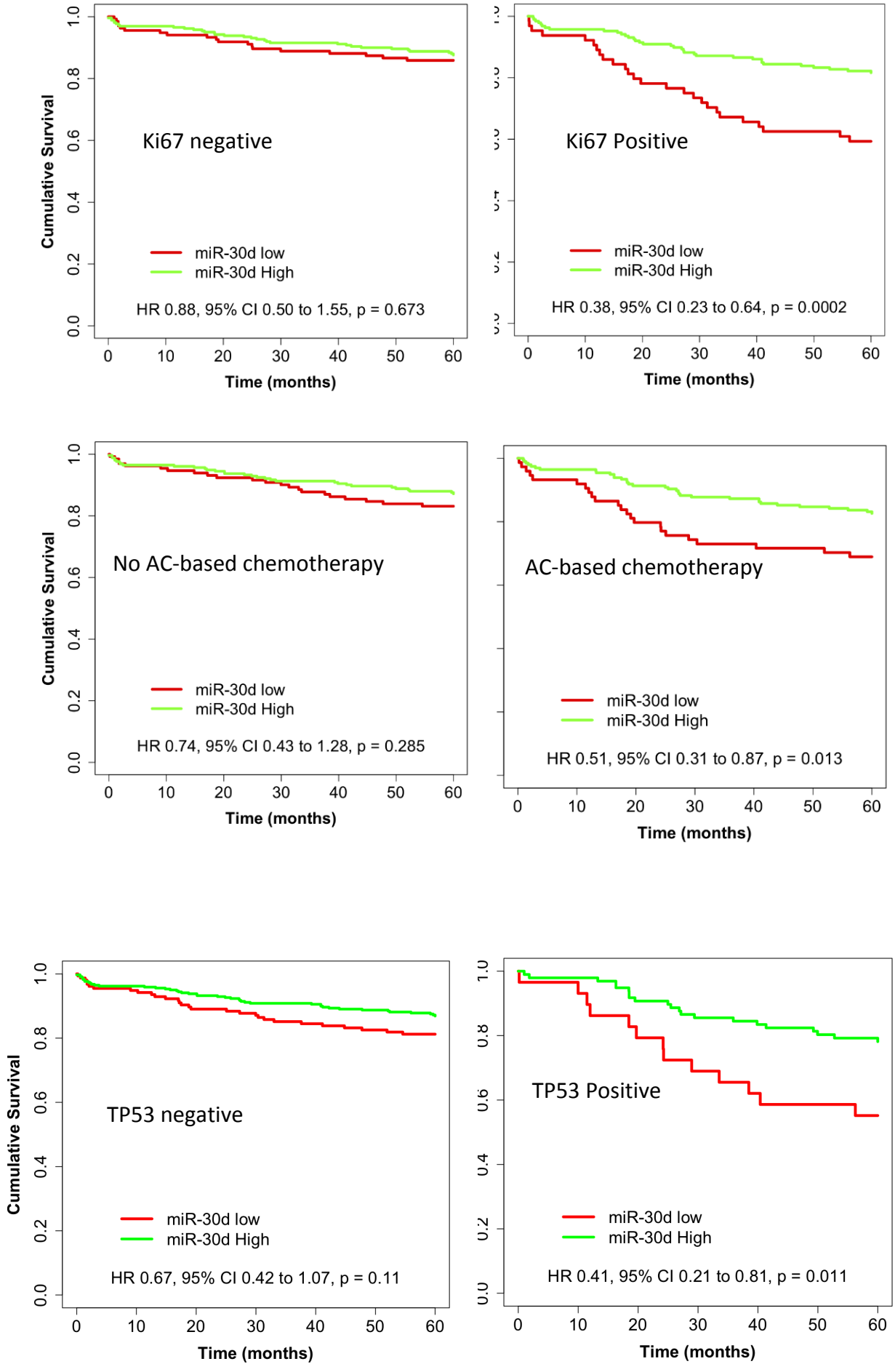
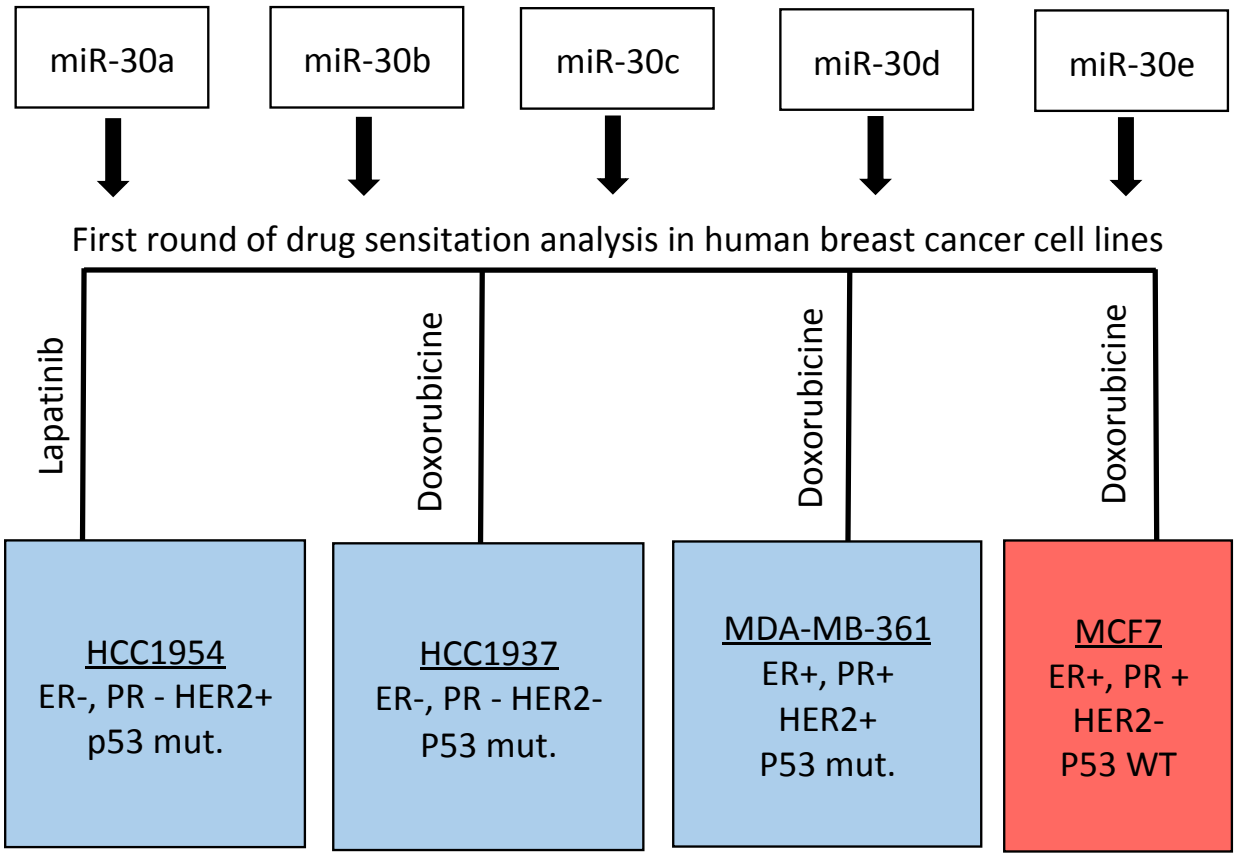
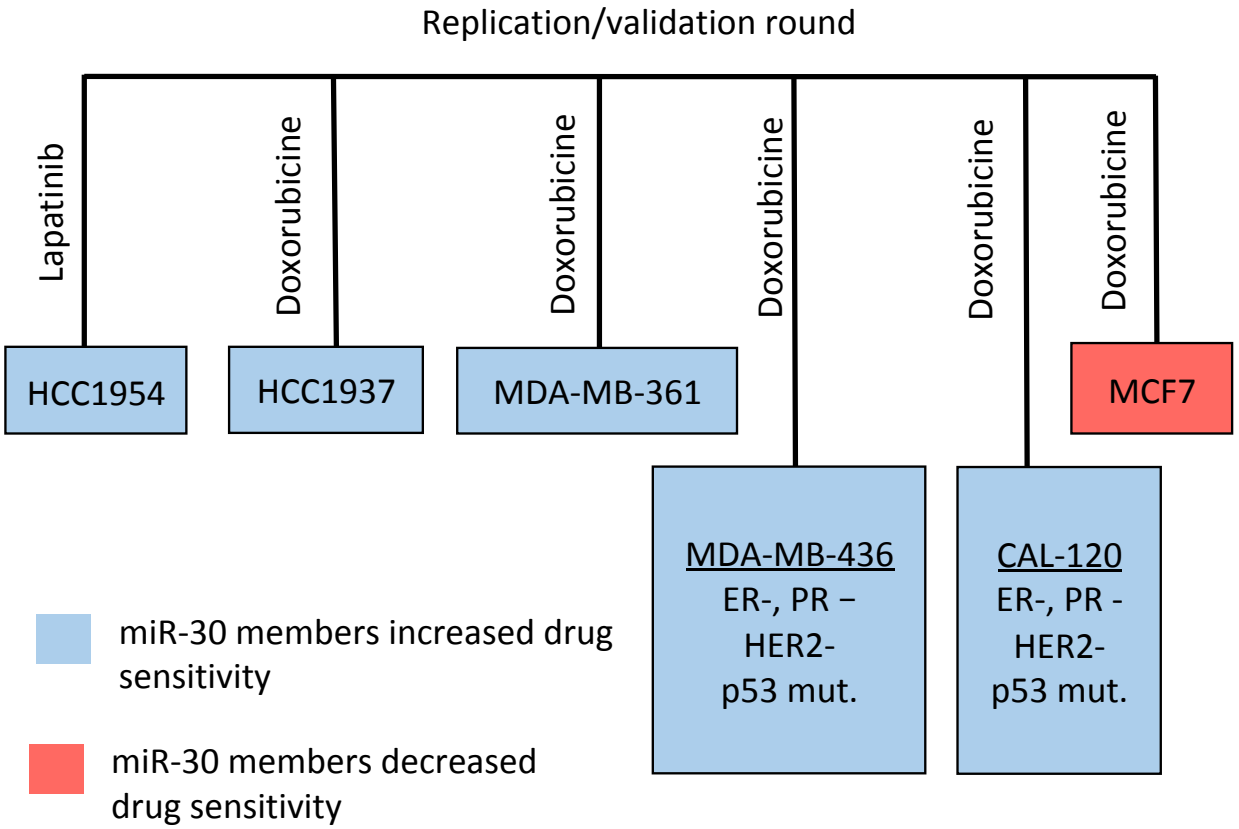


Figure 5. Kaplan–Meier plots of differential survival by miR-30d expression among all patients and in subgroups of ER-negative, ER-positive, HER2-negative, HER2-positive, Ki67-negative, Ki67-positive, no chemotherapy, and chemo-treated cases (unpublished data).

5.4.3 Drug sensitivity screening

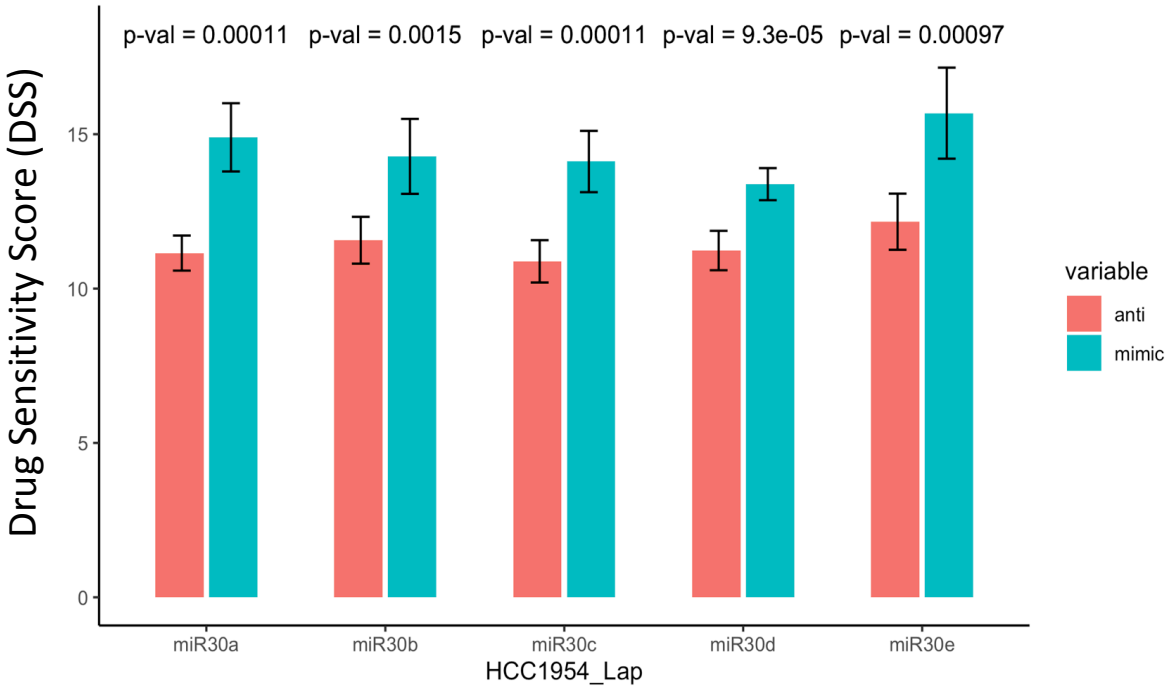
The result of survival analysis in the subset of patients who received anthracycline-based chemotherapy suggested a possible association between miR-30 and anthracycline-based therapy outcomes. No clinical data was available to perform a survival analysis on anti-HER2 outcomes, as the treatment was not used at the time when the studied cohorts were ascertained. However, following the clinical evidence implicating an association between miR-30 expression and patients' survival by HER2 status of the tumors, an exploratory *in vitro* analysis was conducted to investigate the impact of miR-30 family members in response to anti-HER2 treatment. A dose-dependent drug sensitivity screening was conducted testing two drugs: doxorubicin, an anthracycline-based chemotherapy, and lapatinib, a dual inhibitor of HER2. The human breast cancer cell lines involved in doxorubicin screening included HCC1937, MDA-MB-361, MCF7, and the lapatinib screening was performed in HCC1954, which is a HER2-positive breast cancer cell line. In the replication/validation round, in addition to the above-mentioned cell lines, MDA-MB-436 and CAL120 were added to the screening. Figure 6 illustrates the workflow of the primary and the replicatory/validation round of drug screening.

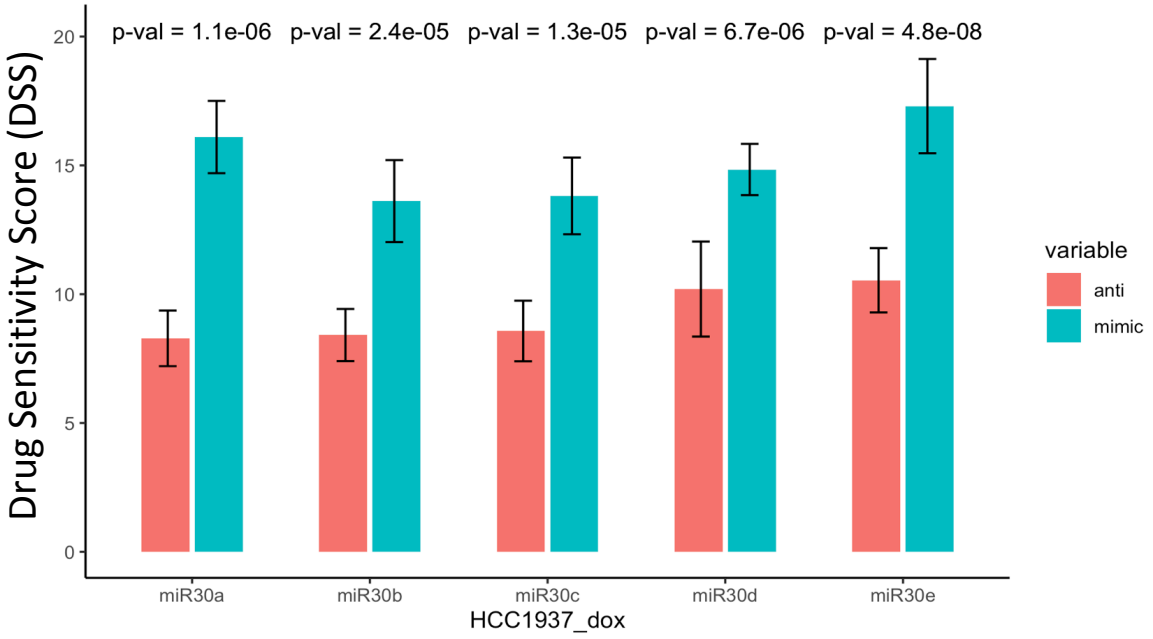

miR-30a
miR-30b
miR-30c
miR-30d
miR-30e
First round of drug sensitation analysis in human breast cancer cell lines
Lapatinib
Doxorubicine
Doxorubicine
Doxorubicine
HCC1954
ER-, PR - HER2+
p53 mut.
HCC1937
ER-, PR - HER2-
P53 mut.
MDA-MB-361
ER+, PR+
HER2+
P53 mut.
MCF7
ER+, PR +
HER2-
P53 WT

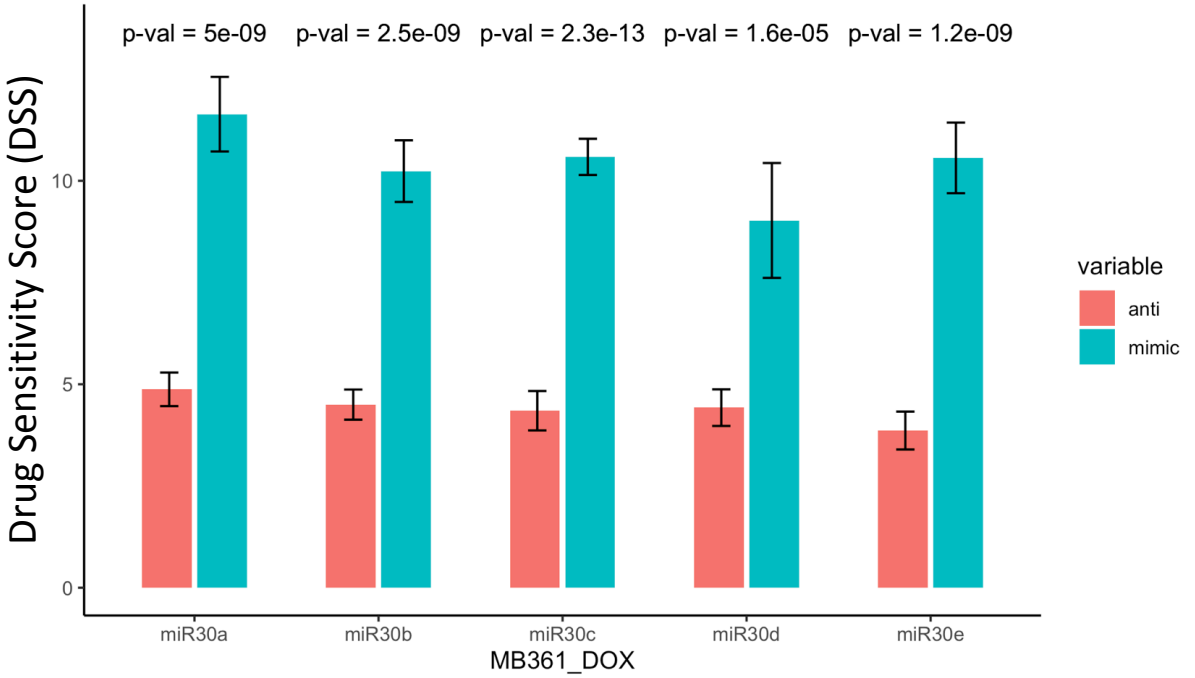

Replication/validation round
Lapatinib
Doxorubicine
Doxorubicine
Doxorubicine
Doxorubicine
Doxorubicine
HCC1954
HCC1937
MDA-MB-361
MCF7
MDA-MB-436
ER-, PR –
HER2-
p53 mut.
CAL-120
ER-, PR -
HER2-
p53 mut.
miR-30 members increased drug sensitivity
miR-30 members decreased drug sensitivity

For each miR-30 family member, i.e. miR-30a–e, a specific miRNA mimic and miRNA inhibitor was acquired (described in section 4.4) and every drug-treated cell line were transfected with either a miRNA mimic or miRNA inhibitor of the studied family member, with 6 replicates in the primary round and 11 replicates in the replication/validation round. The Drug Sensitivity Score (DSS) (Yadav et al., 2014; Fagerholm et al., 2017) measures the drug response based on miR-30-exposed cell viability at increasing drug concentrations.

Figure 7, and *Supplementary Figure 2* in *Study IV,* illustrate the visual comparison of DSS between each miR-30 member compared to its inhibitor per cell line in the primary and replication rounds, respectively. In the first round of screening, all of the miR-30 family members sensitized (indicated by higher DSS) HCC1954 (the HER2+ cell line) to HER2-targeted lapatinib compared to their corresponding inhibitors with *p*-values varying between 1.5e-03 to 9.3e-05. The effect was reproduced in the replication round with *p*-values varying between 1.2e-02 to 4.2e-15. In the HCC1937 (the triple negative, p53-deficient cell line), all miR-30 mimics strongly sensitized the cell line to doxorubicin compared to miR-30 family member inhibitors with *p*-values varying between 1.3e-05 to 4.8e-08. In the replication round, all miR-30 members presented a similar effect with the largest p = 7.5e-07. A consistent effect was observed in the MDA-MB-361 (the luminal-like, p53-deficient, HER2+ cell line), with all miR-30 members sensitizing the cells to doxorubicin compared to their inhibitors in the primary (largest $p < 10^{-4}$) and replication (largest $p < 10^{-6}$) rounds. In MCF7 (the luminal-like, p53-proficient, HER2- cell line), miR-30 members showed an opposite effect, i.e. the miR-30 mimics decreased doxorubicin sensitivity compared to their inhibitors. However, only miR-30d (1.1e-03) and miR-30e (4.9e-02) reached statistical significance. In the replication round with a higher number of replicates, the effect was more pronounced with *p*-values between 0.11 and 1.4e-06. In the replication/validation round, we added two more basal-like, p53-deficient cell lines (MDA-MB-436 and CAL-120) to those included in the primary round. In both cells, all miR-30 members increased the cells sensitivity to doxorubicin compared to their corresponding inhibitors with the largest p = 9.4e-15 and p = 2.5e-06 in MDA-MB-436 and CAL-120, respectively. See *Supplementary Table 3* in *Study IV* for a detailed list of the DSS and the statistical test.


p-val = 0.00011
p-val = 0.0015
p-val = 0.00011
p-val = 9.3e-05
p-val = 0.00097
Drug Sensitivity Score (DSS)
0
5
10
15
miR30a
miR30b
miR30c
miR30d
miR30e
HCC1954_Lap
variable
anti
mimic


p-val = 1.1e-06
p-val = 2.4e-05
p-val = 1.3e-05
p-val = 6.7e-06
p-val = 4.8e-08
Drug Sensitivity Score (DSS)
0
5
10
15
20
miR30a
miR30b
miR30c
miR30d
miR30e
HCC1937_dox
variable
anti
mimic



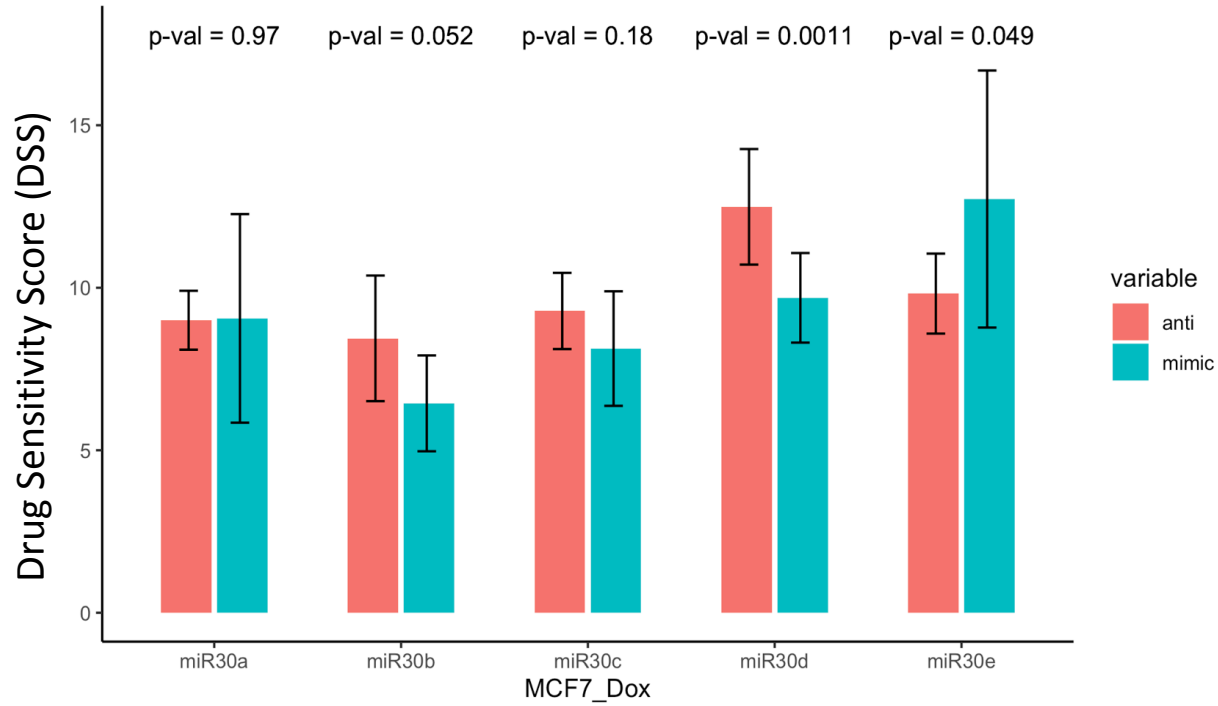


Figure 7. Drug sensitivity scores (DSS) for breast cancer cell lines transfected with miR-30 family member mimics and inhibitors. Higher DSS indicates increased sensitivity to drugs. Student t-test compared DSS between each miR-30 member and its corresponding inhibitor.

5.4.4 Association with gene expression level, and functional annotation

To investigate the association between the miR-30 family members and the expression level of the genes, the publicly available METABRIC breast cancer dataset was applied to 1,302 breast tumors (Dvinge et al., 2013) with two parallel approaches: MicroRNA Target Filter analysis and the Core analysis. For the MicroRNA Target Filter analysis, only the negatively correlated genes were included in the analysis, assuming that the miRNA function on mRNA-level is repressive, whereas in the Core analysis, all correlated genes were included. The Ingenuity Pathway Analysis (IPA, QIAGEN N.V., Venlo, The Netherlands) was used to study the pathway enrichment analysis. Consistent in both Target and Core analyses, the set of genes correlated with miR-30 family members were strongly enriched in pathways of cell migration, motility, and cytoplasmic development. See *Supplementary Table 4* in *Study IV* for the detailed number of correlating genes and pathways per miR-30 member.

6 Discussion

While the impact of germline variation on breast cancer risk has been largely investigated, our understanding of the role of hereditary components in patient's survival and therapy outcome remains incomplete. This work aimed to identify molecular prognostic and predictive markers of breast cancer by screening cancer-related networks (TP53 and NF-κB), and by studying candidate genes in regulatory networks of microRNAs (miR-30 family) and candidate proteins (NQO1 and NF-κB), for their potential contribution to breast cancer survival and treatment outcome. A previous study by Fagerholm et al. (2008) identified an SNP in *NQO1*, rs1800566, which reduces the protein half-life, to predict decreased breast cancer patients' survival, especially after anthracycline-based chemotherapy and in p53-positive (aberrant) tumors. Their findings suggested that NQO1 modifies the anthracycline-based treatment outcome, possibly through a p53 and TNF-NF-κB pathway. That prompted Studies I, II and III to be conducted, investigating the prognostic and predictive potentials of TP53, NF-κB and NQO1, along with the genes involved in their networks. Following the evidence shown by Li et al. (2012) on the association of miR-30d expression with poor clinical outcome in ovarian cancer patients, Study IV was conducted to investigate the prognostic and predictive value of miR-30d, and its family members, in breast cancer.

6.1 TP53 network genes

Study I examined the prognostic association of germline variations in the TP53 network genes, *PRKAG2, PPP2R2B, CCNG1, PIAS1* and *YWHAQ,* which previously had been suggested to modify predisposition to cancer development or patients' survival and drug response (Vazquez et al., 2008, 2010). Additionally, *TP53* R72P and *MDM2* SNP309 variants were investigated for their interaction with the variant in the studied genes following the previous reports on their implication on breast cancer patients' survival (Tommiska et al., 2005; Schmidt et al., 2009). The variants were also studied for their association with pathological characteristics of the tumors. Two variations in the *PRKAG2* gene, *PRKAG2*-01 (rs1029946) and *PRKAG2*-02 (rs4726050), showed suggestive evidence for improved patient survival, however, the effect appeared to be driven by the HEBCS study. The *PRKAG2*-01 (rs1029946) rare G allele emerged as a predictor of survival in the pooled data independently of the conventional prognostic factors, age of diagnosis, and study. For the same SNP, carriership of GG genotype was found to associate with TP53-immuno-negative tumors. *PRKAG2* encodes AMPKγ, the gamma-2 regulatory subunit of AMP-activated protein kinase, which is a highly conserved metabolic sensor across eukaryotes maintaining energy homeostasis (Garcia et al., 2017) and a regulator of TP53 (He et al., 2014) under metabolic stress. AMPK might have a contextual tumor suppressor role by activating the cell cycle arrest or senescence through its interaction with TP53 under glucose shortage. AMPK is reported to activate TP53 by phosphorylating on Serine 15 in low glucose condition to promote G1/S cell cycle arrest (Jones et al., 2005); however, whether that is sufficient for TP53 activation is not confirmed (Chao et al., 2000; He et al., 2014). Under the glucose starvation mode, continuous activation of AMPK provokes TP53-dependent cellular senescence (Jones et al., 2005). In contrary to the plausible tumor suppressor-like impact of AMPK under metabolic stress, it has been suggested that under hypoxia, AMPK pathways may provoke cell survival by favoring adaptation to stressed conditions

in order to maintain energy homeostasis at cellular and body levels (Garcia et al., 2017), possibly by an anti-apoptotic mechanism through LKB1-AMPK interplay. LKB1 plays a central role in maintaining the homeostatic ratio between ATP and AMP via AMPK to inhibit the initiation of apoptosis, thus in this context, LKB1-AMPK exerts a proto-oncogenic function (Jeon, Chandel & Hay, 2012; Laderoute et al., 2006; Lee et al., 2015).

In this context, the association between the rare G allele and improved survival could be interpreted in keeping with the AMPK cell survival function. Interestingly, the gene expression analysis of *PRKAG2* in the HEBCS dataset showed a direct association between high expression of *PRKAG2* and decreased breast cancer patients' survival ($p_{log\text{-}rank\ test}$ = 0.014) (*Supplementary Figure 1* in *Study I*). However, in the microarray dataset of 187 breast cancer cases, no significant correlation was found between the *PRKAG2*-01 (rs1029946) rare G allele and the expression of the gene. Both of the *PRKAG2* SNPs lie within the intronic regions of the genes without any predicted effect on the protein sequence, however, *PRKAG2-02* (rs4726050) is in linkage disequilibrium with *PRKAG2* (rs2727567) which was suggested to modify drug response *in vitro* (Vazquez et al., 2008).

In the test for interaction, a significant (p = 0.001) dose-dependent interactive effect of the *PRKAG2*-02 (rs4726050) with *MDM2* SNP309 emerged as a modifier of patients' survival. Improved patients' survival by *PRKAG2*-02 (rs4726050) was confined to the cases with *MDM2* SNP309 (TG/GG) genotype. While patients' survival did not differ by *MDM2* SNP309 genotypes alone in this study and previous publications (Schmidt et al., 2009; Toyama et al., 2007; Boersma et al., 2006), and only changed with borderline significance (p = 0.049) by *PRKAG2*-02 (rs4726050), the observed effect is likely due to a combined effect. Also, the interaction term emerged as a significant predictor of patients' survival in a multivariate Cox regression model including the SNPs' main effect as well as the interaction term (p = 0.047). SNP309 is a G to T change in the regulatory region intron 1, which directly correlates with the elevated expression of *MDM2* which is a well-documented negative regulator of TP53 (Bond et al., 2004; Karni-Schmidt, Lokshin & Prives, 2016).

An interaction between *MDM2* SNP309 GG genotype and *TP53* 72Pro (compared to Arg72) variant was previously shown to associate with poor patient survival (Schmidt et al., 2009), which is in keeping with *MDM2* SNP309 increasing the *MDM2* level and the Arg72 variant (compared to 72Pro) inducing apoptosis and increasing the pro-apoptotic TP53-regulated genes (Jeong et al., 2010). The underlying mechanism of the observed interaction between *PRKAG2* (AMPKγ) and *MDM2* and how it may affect patients' survival cannot be hypothesized here; however, the result of this study suggests that the genetic variations affecting the major player of metabolic and energy homeostasis, PRKAG2/AMPK, in combination with *MDM2* SNP309, may have an impact on TP53 function and therefore cell survival in breast cancer tumors.

Furthermore, there was suggestive evidence for the association of *PPP2R2B* (rs10477313) AA/AG genotype with improved patient survival (p = 0.034) especially among subgroups based on hormonal therapy (p = 0.014). The SNP was a predictor of improved hormonal therapy outcome independently from the conventional prognostic factors. Another *PPP2R2B* SNP, rs319217, was previously reported to associate with breast cancer recurrence after hormonal therapy (Vazquez et al., 2011). Additionally, the gene expression analysis of *PPP2R2B* in Study I showed association with patients' survival, with *PPP2R2B* low expression correlating with decreased patients' survival

($p_{log\text{-}rank\ test}$ = 0.014) (*Supplementary Figure 2* in *Study I*), which is in line with the suggested tumor suppressor-like function of PP2A. Also, the carriers of AA genotype were frequently among the PR-negative tumors. *PPP2R2B* encodes the regulatory B subunit of the Ser/Thr protein phosphatase 2A (PP2A), which regulates the phosphorylation of proteins involved in cell cycle, DNA replication, cell mobility and apoptosis, and is often inactivated in cancer cells by phosphorylation of Tyr-307 (p-PP2A) (Seshacharyulu et al., 2013). Reduced expression of PP2A occurs in multiple cancer types including those of the breast, often through the promoter hypermethylation (Muggerud et al., 2010). The PP2A complex functions as an inhibitor of signal transduction in the PI3K/AKT/mTOR pathway (Ruvolo, 2016), which is frequently over-activated in cancer cells. Additionally, PP2A activation demonstrated synergy with the inhibitors of PI3K/AKT/mTOR, and their combination resulted in increased cell death of pancreatic cancer cells *in vitro* and *in vivo* (Allen-Petersen et al., 2019).

Given that the aberrant PI3K/AKT/mTOR signaling pathway is among the aromatase inhibitors (AIs) resistance mechanisms (Yamnik et al., 2009; Mills, Rutkovsky & Giordano, 2018), it could have been presumed that PP2A activation might play a role in AI efficacy. Also, AI resistance occurs by the phosphorylation of ERα serine 167 (Ser167), and recent studies showed that the upregulation of PP2A suppresses the Ser167 phosphorylation in an estradiol-dependent manner (Hayashi et al., 2017) which lend further support to the potential relevance of PP2A in hormonal therapy of breast cancer also suggested by the results found in Study I. Overall, Study I provides further evidence for the implications of the genetic variations in genes involved in the TP53 network as potential prognostic and therapeutic markers of breast cancer.

6.2 NF-κB network genes

A two-SNP interaction analysis was performed to evaluate the plausible epistatic/non-additive interactive effects of 917 germline variations in 75 genes involved in the NF-κB activating pathway. The study applied a semi-parametric approach, a large BCAC sample size of n=30,431, and stringent *p*-value and hazard ratio criteria driven from the power analysis for each model of inheritance. Two SNP pairs, rs5996080-rs7973914 (in chromosomes 22 and 12, respectively) and rs17243893-rs57890595 (in chromosomes 9 and 8, respectively), were identified to associate with patients' survival under the recessive and dominant model of inheritance, respectively. None of the SNPs alone showed statistically significant survival effect.

For the recessive SNP pair, rs5996080-rs7973914, the carriership of the homozygous rare allele of both SNPs associated with decreased 10-year overall survival compared to carriers of at least one common allele. No correlation was observed between the interacting genotype combination and tumor's pathological characteristics, which could be partially due to the limited number of the concomitant rare homozygous genotype of both SNPs in each category. The NF-κB related loci represented by the recessive SNP pair include *BAFFR*, indicated by rs5996080 at 31.5kb downstream, and *TNFR1* and *TNFR3*, indicated by rs7973914 at 27kb and 8kb upstream, respectively.

The SNP inclusion criteria in this study involved the variations within or in the 50kb flanking region of genes in the major NF-κB activating pathway. However, physically, rs5996080 lies in the intron of *SREBF2* (sterol regulatory element-binding transcription factor 2), and rs7973914 is located in the intron of *SCNN1A* (sodium channel non-voltage-gated 1 alpha subunit). *SREBF2* encodes *SREBP2* of *SREBP* transcription factor family proteins, which are necessary for cholesterol homeostasis (Ricoult et al., 2016). Little has been reported on the association between *SREBP2* and breast cancer, particularly in an NF-κB dependent manner. However, a study in liver cancer cells showed that lipopolysaccharide (LPS), found in the outer membrane of gram-negative bacteria, and which can trigger inflammatory responses, enhances the cholesterol accumulation by upregulating *SREBF2* through the NF-κB signaling pathway (He et al., 2017). As for *SCNN1A,* which hosts the other SNP in the pair (rs7973914), its aberrant expression level, associating with extensive DNA hyper-methylation, has been shown by an epigenetic biomarker analysis in a cohort of primary breast cancer. Moreover, the SCNN1A protein level appeared to be normal in luminal-like tumors, whereas it was reduced in triple negative subtypes (Roll et al., 2013).

In keeping with the interactive association of the two loci represented by this SNP pair, Study II also identified an rs5996080 proxy (rs5996088 $r^2 = 1$) which correlated with lower expression of both *SREBF2* and *SCNN1A* ($p = 0.014$ and $p = 0.0007$ respectively; TCGA dataset only). Similarly, rs5996080 proxies showed significant correlation with the expression level of both of the candidate NF-κB related genes in the same loci, i.e. *BAFFR* and *TNFR1/3*, represented by the recessive SNP pair.

The protein product of *BAFFR* is a specific receptor of BAFF, which is a pivotal component for the survival of maturing B lymphocyte, and an activator of the non-canonical NF-κB pathway (Zhang, Lenardo & Baltimore, 2017). *NF-κB1* and *NF-κB2* encode p105 and p100, respectively, which are processed to the active forms of p50 and p52 NF-κB subunits, respectively. BAFF/BAFFR play a major role in promoting the processing of RelB/P100 to ReLB/P52 through the stabilization of the IKK complex in a NEMO-independent manner (non-canonical pathway) (Claudio et al., 2002), resulting in translocation of NF-κB2 into the nucleus and its corresponding pro-survival effects (*Figure 3* in *Study II*).

While the BAFF-induced inflammatory background in cancer patients has been postulated to associate with cancer cachexia (Rihacek et al., 2015), its role in breast cancer development and the clinicopathological characteristics and evolution of the disease remains to be elucidated. A small immunohistochemistry study on 52 human breast cancer samples found no differential expression of BAFF among normal and cancer tissues. Also, BAFF expression did not associate with disease-free survival or the overall survival of patients (Pelekanou et al., 2008). Similarly, in Study II, the SNP representing the BAFF receptor did not show any survival association alone. It has been suggested that BAFFR, along with BCR (B cell antigen receptor), influence NF-κB activation also through the canonical pathway; however, the magnitude of its impact is yet to be investigated (Siebenlist, Brown & Claudio, 2005; Morrison et al., 2005).

The other genes represented by the recessive SNP pair, *TNFR1* and *TNFR3,* encode for receptor types 1 and 3, respectively. Similarly to BAFFR, these are transmembrane glycoproteins and members of the TNF receptor superfamily (Fuchs et al., 1992; Sennikov et al., 2014). In response to their corresponding form of TNFα ligands, TNFR1 and TNFR3 activate the canonical or non-

canonical NF-κB pathway which, depending on the cellular context and the protein domains of the molecular mediators involved, results in promoting proliferation, apoptosis, or increased cytotoxicity (*Figure 3* in *Study II*) (Zhang, Lenardo & Baltimore, 2017; Wajant, Pfizenmaier & Scheurich, 2003). Given that many biological impacts of TNFα are realized through TNFR1, it could be postulated that the alteration in the function of this protein and its interacting partners may disturb the dynamics between the pro- and anti-survival NF-κB signaling pathways, which may consequently modify cancer progression, possibly in an epistatic manner. Although the underlying mechanism of the SNP-SNP interaction effect observed here can only be speculated at this point, the association between the recessive SNP pair or their proxies, particularly rs5996080, with the expression level of both BAFFR and *TNFR1/3* lends further support to the possible combined effect of the represented loci on patients' survival. While the result of this study is in line with the suggested pro-survival role of BAFF/BAFFR and TNFR1/3 (Almaden et al., 2014; McClements et al., 2008; Legler et al., 2003), all these receptors have also been shown to induce anti-survival signals depending on the involved receptor interactive proteins, particularly TNFα which is essentially a pleiotropic cytokine (Hehlgans & Pfeffer, 2005; Hsu, Xiong & Goeddel, 1995; Hsu et al., 1996). It could be presumed that the controversies may also be due to the complexity of the pathway itself as well as the diverse biological effects of its stimuli.

For the dominant SNP pair, rs17243893 and rs57890595, the carriership of at least one rare allele for both SNPs improved 10-year breast cancer survival compared to the carriers of the homozygous wild-type genotypes. Patients' survival did not differ by either of the SNPs alone. In line with the survival result, the protective genotype combination associated with negative nodal status, and negative distant metastasis at diagnosis.

The first SNP of the pair, rs17243893, lies in the intronic region of *TRAF2*, which encodes TRAF2, a frequent target of pro-inflammatory and tumor-derived mediators and activators of the NF-κB signaling pathway (Shen et al., 2015). Upon activation of the upstream TNF receptors, TRAF2 forms a multimeric complex which initiates a kinase cascade to transduce the NF-κB activating signal through the IKK complex (Zhao et al., 2015). Several studies implicated the role of TRAF2 in cancer (Thomas et al., 2009; Wood et al., 2012), including its upregulation in the malignant pleural effusion cells in human breast cancer and its association with decreased patient survival (Zhao et al., 2015). Another study has reported the elevated copy number of TRAF2 in epithelial cancers, including those of the breast (Shen et al., 2015).

The other SNP in the dominant pair, rs57890595, resides in the intron of TRAIL receptor *TRAIL-R4*, which is involved in the activation of the NF-κB pathway through a TRAF2-NIK-IKK complex (*Figure 3* in *Study II*), which results in pro- or anti-apoptotic outcomes depending on the TRAIL receptor from which the signal originates (Lalaoui et al., 2011; Nguyen et al., 2018). In brief, TRAIL-R1/2 induce cell death signals, whereas TRAIL-R4 seems to be restricted to non-apoptotic pathways. It can be presumed that the anti- or pro-survival signal transduced through the TRAIL receptors bifurcate at the TRAF2 step which, in addition to the often reported pro-survival effect of TRAF2 and TRAIL-R4, is consistent with the observed interaction between the carriership of the combined rare allele and improved patients' survival in Study II. However, the study conclusion is also limited because none of the SNPs in the dominant pair, nor their proxies, were represented in

the METABRIC/TCGA database to evaluate the association between this pair and *TRAIL-R4* and *TRAF2* expression.

Another weakness of this study is the potential data interpretation biases generated by pathway-based SNP selection: the regulatory association of the selected SNPs may extend beyond their cis haplotype and thus, the causal gene exerting the observed survival association may not have been integrated in the study hypothesis. To address this problem within the means of this study, a genome-wide gene expression association study was performed for the studied SNPs and their proxies, and no significant correlation was observed with other genes elsewhere. However, since the SNP pairs in the recessive model are physically located in two other genes in the same loci, *SREBF2* and *SCNN1A,* and in light of the observed correlation between an rs5996080 proxy (rs5996088) with the expression of *SREBF2* and *SCNN1A,* as well as *BAFFR* and *TNFR1/3,* the interaction effect cannot be exclusively attributed to the *NF-κB* genes. Furthermore, large-scale analyses are potentially at risk of inflated type I error. To limit the probability of false positive results, the study power was calculated to define robust HR thresholds, and appropriate multiple testing correction methods were applied.

6.3 NQO1 and NF-κB

A study by Fagerholm et al. (2008) found strong association between the homozygous missense variant of NQO1 (rs1800566, P187S) and patients' survival, especially in the subset of patients who received anthracycline-based chemotherapy and among the cases with TP53-positive immunohistochemistry (suggestive of mutant TP53). The homozygous rare T allele disables NQO1 activity and possibly disturbs its ability to stabilize major stress response proteins such as TP53 or to regulate the NF-κB pathway (Asher et al., 2005).

Study III analyzed the immunohistochemical staining of NQO1 expression and NF-κB nuclear localization in two series of breast cancer tumors for prognostic, predictive, and clinicopathological association. No significant impact on patients' survival or treatment outcome was observed by the expression of NQO1 or the nuclear localization of NF-κB (inferred activity). However, an inverse correlation was found between NQO1 expression and NF-κB nuclear localization. The inverse pattern of correlation was also seen in their association with ER status of the tumors, i.e. negative NQO1 expression and positive NF-κB nuclear localization were found more frequently in ER-negative tumors than in ER-positive tumors. Consistently, the adverse correlation between NQO1 and NF-κB was also reflected in the microarray gene expression analysis results, as well as the functional annotation of the associating genes. Interestingly, among the genes which positively correlated with *NF-κB*, and thus negatively with *NQO1*, were genes involved in the immune response as well as those which are NF-κB nuclear import promoting factors such as *TNF*, *TNF*-related genes and *TLR*-related genes (Zhang, Lenardo & Baltimore, 2017). Of genes which positively correlated with *NQO1,* and negatively with *NF-κB*, were those implicated in cellular processes of oxidation/reduction, and steroid metabolism consistent with the published functions of NQO1 and the results of this study.

Moreover, the gene expression analysis revealed the co-upregulation of NQO1 and multiple genes involved in steroid metabolism (*Figure 4* and *Supplementary Table 6* in *Study III*), which is in line with the observed association between NQO1 and ER expression in breast cancer tumors. This was also in line with previously published regulatory crosstalk between ER and NQO1 (Carroll et al., 2006), but in contrary to the reported inverse regulatory relationship between ER and NRF2, a positive transcription factor of NQO1 (Mutter, Park & Copple, 2015; Yao et al., 2010). Additionally, tumors with nuclear expression of *NF-κB* were frequently ER-negative, which is consistent with the published mutually-suppressing crosstalk between ER and NF-κB (Biswas et al., 2004). Several studies had reported the co-activation of NQO1 and NF-κB in normal and skin cancer cells (Cheng et al., 2010; Iskander et al., 2006; Ahn et al., 2006).

The results of Study III point to an inverse correlation between the two proteins, which might be explained by their suggestive opposite connection with ER signaling in breast cancer. The adverse correlation may also be due to the molecular link between NQO1, NF-κB and TP53. Indeed, it has been shown that TP53 degradation, induced by NQO1 deficiency, elevates the nuclear level of NF-κB in prostate cancer cells, possibly by competing for the limited pool of their transcriptional co-activator proteins, p300 and CBP (Thapa et al., 2014). Nevertheless, in-depth functional follow-up is required to confirm and investigate the biological explanation behind the reverse correlation observed here.

6.4 miR-30 family

In Study IV, the miRNA *in situ* hybridization was applied to analyze the cytoplasmic expression of miR-30d for its relation to clinicopathological and survival data in 1,238 human breast cancer tumors. High expression of miR-30 was a predictor of longer metastasis-free survival and breast cancer survival, independently of the conventional prognostic markers. The survival association was especially pronounced among subgroups with Ki67 positivity (inferred high proliferation), with ER negativity, those who received chemotherapy, and among patients with HER2-positive tumors.

On the basis of the observed survival association of miR-30d by HER2 status and the suggestive evidence of its association with anthracycline-based therapy outcomes, and given that all the miR-30 family members (miR-30a–e) share the mature seed regions, the study further investigated the impact of all miR-30 members on response to lapatinib and doxorubicin *in vitro*. The association between high expression of miR-30d and improved survival in HER2-positive subgroups was in keeping with the miR-30 family members sensitizing the HER2+ HCC1954 cell line to lapatinib. Considering that in breast cancer the TOP2A amplification usually occurs with HER2 amplification, and given that TOP2A is the primary target of anthracycline-based drugs (Brase et al., 2010; Arriola et al., 2007; Di Leo et al., 2002; Villman et al., 2006; Jacot et al., 2013), it could be postulated that a miR-30/HER2/TOP2A axis in breast cancer tumors may influence doxorubicin (anthracycline-based agent) sensitivity, as well as the lapatinib response due to its HER2-targeting mechanism. In the subset of patients receiving anthracycline-based chemotherapy, high miR-30d associated with improved patient survival. In the drug sensitivity screening, the miR-30 family member mimics strongly sensitized the breast cancer cell lines to doxorubicin compared to their inhibitors. This result is in line with previous studies reporting the inhibition of chemoresistance by

miR-30 family members in a variety of cancers, including those of the ovaries (Sestito et al., 2016) and breast (Fang et al., 2014; Bockhorn et al., 2013).

In this study, the effect of miR-30 members on drug sensitivity was consistent in all of the cell lines except for MCF7 which exhibited an opposite effect, i.e. the miR-30 family member mimics decreased cell line sensitivity to doxorubicin compared to their inhibitors. Given that MCF7 is the only p53-proficient cell line in the screening, it can be postulated that the observed opposite effect might be associated with its p53 status. In the survival analysis, high miR-30d also associated with better survival among patients with p53+ (mutated) tumors. The TP53 mRNA expression and protein activity were not available in the METABRIC dataset to further analyze the miR-30 family and p53 activity. However, several lines of evidence have demonstrated miR-30a as the direct target of p53, and its reduced expression has been reported to associate with poor patient survival (Guo et al., 2016; di Gennaro et al., 2018, 2019). Additionally, it has been suggested that p53 inhibits the expression of ZEB2, a transcriptional factor involved in EMT (a key molecular step of metastasis) (Mittal, 2018), through miR-30a to control tumor cells' invasion and dissemination (di Gennaro et al., 2018, 2019). Here, the pathway enrichment analyses found a negative correlation between miR-30 and genes involved in cell motility and migration, which is also in line with our clinical findings of high miR-30d association with longer metastasis-free survival.

Several studies suggest that miR-30 family members inhibit cell migration and invasion by suppressing EMT and cell mobility phenotypes in cancers, including breast carcinoma (Zhang et al., 2014; Kao et al., 2014; Cheng et al., 2012), particularly through their interaction with SNAI1 and SNAI2 (Kumarswamy et al., 2012; Zhou et al., 2013) and metadherin (Zhang et al., 2014). Furthermore, our findings in breast cancer contradict the study by Li et al. (2012) in ovarian cancer, which suggested an inverse association between high miR-30d expression and ovarian cancer patients' survival. It appears that the association between miR-30 family members and cancer prognosis, as well as metastasis, might be tissue-dependent and cancer-specific. For instance, unlike in breast cancer, miR-30 family members have been shown to induce metastasis in melanoma (Gaziel-Sovran et al., 2011) and hepatocellular carcinoma (Yao et al., 2010). Thus, the connection between *miR-30* expression and the magnitude of tumor malignancy and patients' survival appears to be cancer-specific.

A weakness of this study is the absence of endogenous miR-30 expression measurement in the drug sensitivity screening, which could have provided a more accurate setting for comparison of the miRNA effect among cell lines, especially between the p53 deficient and proficient cells, as well as among HER2+ and HER2- cell lines. Nevertheless, the postulated connection between the miR-30 effect on drug screening through the HER2/TOP2A axis or p53 and cell migration connection must be viewed as hypothesis generating. Whether the clinical findings of this study are caused by miR-30-induced drug sensitivity due to a plausible connection to proliferation and the HER2/TOP2A axis, p53 status of the tumor cells, or to the postulated anti-metastatic function of miR-30 remains to be further studied.

7 Summary and conclusions

The aim of this thesis was to identify molecular prognostic and predictive markers in breast cancer. Taking two approaches of network screening, and candidate gene study, this work has investigated cancer-related networks (TP53 network, NF-κB activating network), candidate NQO1 protein, and miR-30 family members, to identify prognostic and predictive markers of the disease that could be used to identify subgroups of patients who do or do not benefit from chemo- or endocrine therapy options.

For years the role of TP53 in breast cancer, and cancers in general, has been under extensive investigation. While the impact of somatic *TP53* mutation in breast cancer risk is rather well established, the clinical relevance of germline mutation in *TP53* as a modifier of patients' survival is yet to be clarified (Schon & Tischkowitz, 2018). Given the complex activities of TP53 and its large network of interacting genes, which influence major cancer-related phenotypes, and on the basis of previous evidence suggesting clinical implications for TP53 network genes (Vazquez et al., 2011) and their interaction (Schmidt et al., 2009), this study investigated the association between candidate TP53 related genes and patients' survival and therapy outcome. The survival analysis of 4,701 invasive breast cancer cases found evidence of superior 10-year overall survival for patients carrying the rare alleles of *PRKAG2* (rs4726050) (driven by HEBCS) and *PRKAG2* (rs1029946), and the interaction between *PRKAG2* (rs4726050) with *MDM2* SNP309 emerging as a significant modifier of patients' survival. Additionally, increased patient survival after hormonal therapy was predicted by an SNP in another TP53 network gene: *PPP2R2B* (rs10477313). However, the rare allele of rs10477313 also showed borderline significant correlation with PR negativity, i.e. more often among tumors with a PR-negative receptor. The result of this study warrants further research to investigate and validate the observed effect (Jamshidi et al., 2013).

A two-SNP interaction analysis of germline variations in NF-κB activating pathways among 30,431 invasive breast cancer cases found two interacting SNP pairs associating with patients' survival: under the recessive model of inheritance, patients simultaneously homozygous for the rare alleles of rs5996080 and rs7973914 had decreased survival, and under the dominant model of inheritance, patients carrying at least one rare allele for rs17243893 and rs57890595 showed increased survival. The NF-κB related genes represented by these pairs included *BAFFR* and *TNFR1/TNFR3* for the recessive SNP pair, and *TRAF2* and *TRAIL-R4* for the dominant SNP pair. However, the recessive SNP pair (rs5996080 and rs7973914) physically reside in two other genes in the loci, *SREBF2* and *SCNN1A*, respectively, and an rs5996080 proxy was found to correlate with the expression of all four genes. Therefore, the interacting effect observed under the recessive model cannot be exclusively attributed to the NF-κB related genes. The predictive value of the identified SNP pairs and the biological explanation behind it warrant further studies and comprehensive functional investigations (Jamshidi et al., 2015).

An immunohistochemical analysis of tissue microarray in two series of 1,240 and 283 Finnish invasive breast cancer tumors found an inverse correlation between NQO1 protein expression and NF-κB activation, underlined also by inverse patterns of association with ER and gene expression profiles of tumors, which might be cancer-specific. Neither NQO1 protein expression nor NF-κB nuclear localization emerged as significant predictors of patients' survival (Jamshidi et al., 2012).

A microRNA *in situ* hybridization analysis in 1,238 Finnish invasive breast cancer tumors found that while high expression of miR-30d correlates with highly proliferative tumors, it also strongly predicts longer metastasis-free and breast cancer patients' survival. The survival association was particularly evident in subgroups of patients with HER2-positive or highly proliferating tumors (estimated by Ki67), and among those who have received chemotherapy. In a drug sensitivity screening, miR-30 family members sensitized the breast cancer cell lines to doxorubicin and lapatinib. In the pathway enrichment analysis, the top function of the genes correlating with miR-30 family members was cell movements, which is in line with the observed association between high miR-30d and longer metastasis-free survival, as well as the previously published profile of the miR-30 family. These results suggest that the expression of miR-30 family members may contribute to the prognosis of breast cancer and to the therapy response in a cancer-specific manner. However, estimating the extent of their impact and their predictive value requires further studies.

This work provides suggestions for the potential of germline variants, and their interactions, in *TP53* and *NF-κB* network genes, as well as the expression of miR-30 family members to impact the prognosis of breast cancer and treatment outcome. The findings of this study warrant further investigation. Future association studies followed by in-depth functional investigations can accelerate the identification of objective predictive and prognostic markers of breast cancer. In turn, the discovery of robust predictive markers will facilitate therapeutic decisions and improve patients' care. In general, if further validated and approved reliable, the identified biomarkers might benefit three groups: (1) patients would benefit from personalized and sufficient therapy and avoid the toxicity and side-effects of unnecessary treatments; (2) physicians would be able to customize treatment to each patient's need in a shorter time; and (3) clinics could reduce treatment costs by moving from trial-and-error chemotherapy to rationalized/personalized therapy.

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